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UTILIZATION AND EFFECTIVENESS OF ABCIXIMAB WITHIN ONE-YEAR OF  
PERCUTANEOUS CORONARY INTERVENTION IN ALBERTA

by

CYNTHIA MARY WESTERHOUT



A thesis submitted to the Faculty of Graduate Studies and Research in  
partial fulfillment of the requirements for the degree of Master of Science in

MEDICAL SCIENCES- PUBLIC HEALTH SCIENCES

Edmonton, Alberta  
FALL 2001





UNIVERSITY OF ALBERTA

Faculty of Graduate Studies and Research

The undersigned certified that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled *Utilization and Effectiveness of Abciximab within One-Year of Percutaneous Coronary Intervention in Alberta* submitted by *Cynthia Mary Westerhout* in partial fulfillment of the requirements for the degree of *Master of Science in Medical Sciences—Public Health Sciences*.





To my  
Dad and Mom



## ABSTRACT

**Background:** Abciximab impedes platelet aggregation and is indicated for patients undergoing percutaneous coronary intervention (PCI). **Objectives:** To determine the utilization of abciximab and its effects on one-year mortality and revascularization rates in 2751 Alberta residents who underwent their first PCI in 1999. **Methods:** Descriptive analyses were used to determine utilization patterns. Logistic regression models were used to define risk scores and risk indices for death and revascularization and determine risk-adjusted associations of abciximab with death and revascularization. **Results:** Overall, 43.5% of the patients received abciximab. Patterns of abciximab use differed across institutions and by definitions of risk. Neither risk-adjusted mortality rates (3.8%(abciximab) vs 3.1%(no abciximab)  $p>0.05$ ) nor revascularization rates ((16.7% vs 15.4%)  $p>0.05$ ) were affected by abciximab use. **Conclusions:** Utilization of abciximab was not associated with the risk of death or revascularization within one year of PCI. Risk-adjusted rates of mortality and revascularization were not reduced in patients who received abciximab.





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## LIST OF ABBREVIATIONS

Abx:	Abciximab (ReoPro <sup>®</sup> ).
ACS:	Acute coronary syndromes.
APPROACH:	Alberta Provincial Project for Outcomes Assessment in Coronary Heart disease.
ASA:	Acetylsalicylic acid.
CABG:	Coronary artery bypass graft surgery.
CAD:	Coronary artery disease.
CCS:	Canadian Cardiovascular Society.
CHF:	Congestive heart failure.
COPD:	Chronic obstructive pulmonary disease.
CVD:	Cardiovascular disease.
(k)Da:	(kilo) Daltons
ECG:	Electrocardiogram.
Ept.	Eptifibatide (Integrelin <sup>®</sup> ).
GI:	Gastrointestinal.
GP IIb/IIIa:	Glycoprotein IIb/IIIa receptor (found on platelets).
IABP:	Intra-aortic balloon pump.
LAD:	Left anterior descending artery.
LCA:	Left coronary artery.
LVEF:	Left ventricular ejection fraction.
MI:	Myocardial infarction.
NYHA:	New York Heart Association.
PCI:	Percutaneous coronary intervention (includes both angioplasty and stent).
PTCA:	Percutaneous transluminal coronary angioplasty.
PVD:	Peripheral vascular disease.
RCA:	Right coronary artery.
Tiro:	Tirofiban (Aggrastat <sup>®</sup> ).
UA:	Unstable angina.
V-gram:	Ventriculogram.



## CHAPTER 1: INTRODUCTION

### 1.1 CARDIOVASCULAR DISEASE AND ISCHEMIC HEART DISEASE IN THE WORLD, CANADA, AND ALBERTA

Of the 365 days of the year, St. Valentine's Day brings to mind the images of red roses and star-crossed lovers. However, for millions of people around the world 'matters of the heart' are woven into the fabric of everyday life in the form of ischemic heart disease, a member of the cardiovascular disease (CVD) family.

Cardiovascular disease is considered one of the leading causes of death worldwide. The World Health Organization (WHO) estimated that 30% of all deaths in 1999 were due to cardiovascular disease, which makes CVD the leading cause of death (WHO 2000). In terms of its impact in Canada, approximately 38% of all deaths in 1996 were attributed to CVD (Global Cardiovascular Infobase 2000).

Under the umbrella of CVD, ischemic heart disease includes clinical presentations ranging from angina pectoris (stable and unstable) to myocardial infarction to sudden coronary death (Topol 1998). Ischemic heart disease prevailed as the largest contributor to all CVD-related deaths worldwide (58.1%; 1999) and in Canada (55.4%; 1996) (WHO 2000, Global Cardiovascular Infobase 2000). The age-standardized (to the standard world population (WHO)) mortality rate due to ischemic heart disease in Canada was 110.3 per 100 000 for men and 52.1 per 100 000 for women in 1996. Men and women in Alberta came in slightly below the national rates at 103.8 per 100 000 and 50.4 per 100 000, respectively (Global Cardiovascular Infobase 2000).



Acute coronary syndromes represent a spectrum of acute clinical presentations of ischemic heart disease. In this chapter, a brief overview of the pathophysiology, clinical presentation and therapeutic options for patients suffering from these syndromes is presented. This discussion provides a context for the importance of a novel class of anti-platelet agents known as the glycoprotein IIb/IIIa inhibitors.

## 1.2 BACKGROUND

### *1.2.1 Pathophysiology of Acute Coronary Syndromes*

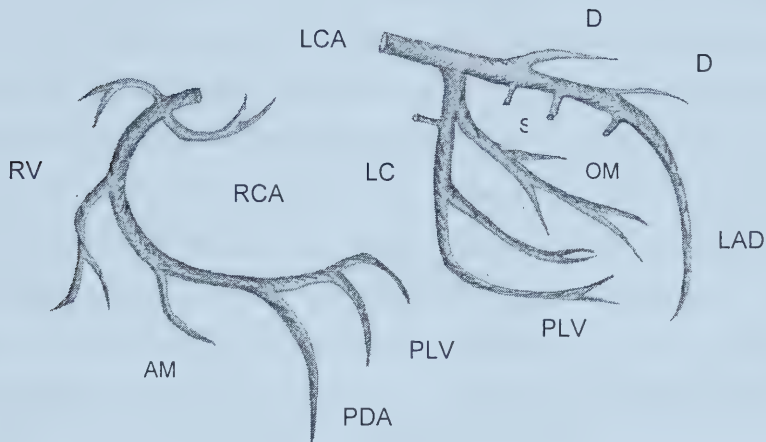
Acute coronary syndromes (ACS) patients can present with varying degrees and durations of myocardial ischemia, which can manifest as unstable angina or myocardial infarction. This variation challenges the precision of diagnosis and hence, the application of treatment strategies. Fortunately, in the last three decades of the 20<sup>th</sup> century, efforts in the basic medical sciences has revealed that this continuum of pathology may be united by a single underlying cause: Thrombosis formation on a fissured or disrupted atherosclerotic plaque (Ambrose and Weinrauch 1996, Libby 2000). Myocardial infarction is the consequence of an acute total occlusion of the artery, whereas unstable angina results from a transient or incomplete occlusion.

From infancy, fatty conglomerates build up on vascular walls in areas of high shear stress and oscillation, such as the outer wall of a coronary artery bifurcation and the inner wall of a curved segment of an artery (Richardson et al 1989, Stary 1989). When considering the anatomy of the heart, the right coronary artery (RCA) has fewer branches than the left coronary artery (LCA), and as a result the majority of target vessels are found in the LCA (Figure 1.1) (Ambrose and Weinrauch 1996).





Figure 1.1. Schematic representation of the right and left coronary arteries (in the left anterior oblique and right anterior oblique projections, respectively).



RCA, right coronary artery; SNA, sinus node artery; RV, right ventricular; AM, acute marginal; PDA, posterior descending artery; PLV, posterior left ventricular; LCA, left coronary artery; LC, left coronary; OM, obtuse marginal; LAD, left anterior descending artery; D, diagonal; S, septal. (Adapted from Topol EJ, ed. Textbook of Cardiovascular Medicine. Philadelphia: Lippincott-Raven Publishers, 1998.)

Based on discoveries during a large series of autopsies, Stary and colleagues (1995) classified plaques into five types, known as the American Heart Association Types I through V. Most of these fatty deposits are non-obstructive, local adaptations to mechanical forces. However, when a stable plaque transforms into an unstable culprit plaque, the threat to coronary flow is initiated. This culprit plaque is characterized by the formation of a fibrous cap over the pre-existing lesion. Inside, several thick layers of connective tissue and numerous inflammatory cells such as macrophages surround the lipid core. The vulnerability of the plaque is determined by the consistency of its contents, the thickness of the fibrous cap and the amount of inflammatory activity in the inner core (Patel and Topol 1999). Plaques that have a high concentration of cholesteryl esters are quite fluid, and thus impart additional stress on the capsule (Ambrose



and Weinrauch 1996). The fibrous cap thins as the arterial source of collagen is depleted with the extinction of smooth muscle cells.

As a result of the actions of the inflammatory substances, endothelial dysfunction can be induced. Endothelial dysfunction can be graded into three types (Ip et al 1990). Type I involves changes in endothelial function but without considerable morphological changes. This level of injury leads to the accumulation of lipids and macrophages. The progression to Type II brings about the release of toxic products by the adjacent macrophages, which results in endothelial denudation and injury to the intima. This is also the point of initiation of platelet adhesion at the injury site. Concurrently, macrophages and platelets release several different substances to initiate migration and proliferation of smooth muscle cells.

Type III endothelial injury is characterized by damage to both the intima and media of the vessel. Also, physical disruption of the thin capsule surrounding the lesion can occur in one of two ways, by erosion or rupture. During the erosion process, the endothelial cells on the plaque exterior are attacked and injured by highly activated macrophages in two manners. Firstly, the macrophages can induce endothelial cell death by apoptosis; and secondly, the endothelial cells can be cut loose from the vessel wall by macrophage proteases (Davies 2000). As a result of the ulceration, large sections of the sub-endothelium become exposed to the lumen of the vessel and provide an adhesion site for a monolayer of platelets (Patel and Topol 1999).

Like endothelial erosion, the root of the pathology of plaque rupture lies in the enhanced inflammatory activities within the plaque, which enlarges the lipid core and applies more stress on the fibrous cap. During plaque rupture, the cap tears and the lipid core becomes exposed to the lumen of



the vessel. Macrophages also attempt to degrade the structural integrity of the plaque by inducing smooth muscle cell death and reducing collagen synthesis (Davies 2000). These actions rapidly degrade the structural integrity of the plaque cap and as a result, lead to rupture.

The rupture of the plaque initiates the cascade of events leading to thrombosis. The lipid arm waves freely in the lumen of the artery and attracts numerous platelets. Exposure of the sub-endothelial layers of collagen and von Willebrand factor also attracts circulating platelets to the injury site. Upon adhesion to the sub-endothelial matrix, platelets are activated and begin to secrete substances that precede chemotaxis, vasoconstriction and activation of other platelets (Patel and Topol 1999). These substances include platelet agonists (adenosine triphosphate (ATP), serotonin, fibrinogen, von Willebrand factor, P-selectin), mitogens (platelet-derived growth factor (PDGF),  $\beta$ -thromboglobulin ( $\beta$ -TG), platelet factor 4 (PDF-4), transforming growth factor  $\beta$  (TGF- $\beta$ ), thrombospondin (TBS)), and proteins that inhibit endogenous clot lysis (plasminogen activator inhibitor-1 (PAI-1)) (Chronos et al 1999).

Activated platelets also undergo dramatic structural reformation. Glycoprotein IIb/IIIa (GP IIb/IIIa) receptors are expressed on the surface of the newly activated platelet in generous amounts (e.g., 40 000 to 50 000 receptors per platelet). These receptors have a high affinity for sub-endothelial proteins, collagen, fibrinogen and von Willebrand factor, which acts to cross-link platelets and promote the formation of a 'white thrombus' (Ferguson et al 1998). In the final stages of thrombosis, red blood cells congregate around the outer layer of this mass, and together with vasoconstriction, the "red thrombus" will occlude the coronary artery. The function of this activated receptor represents the final common pathway of platelet aggregation and hence, thrombus formation (Becker 1999).





The impact of thrombosis manifests itself in clinical presentation. Repeated ulcerations and healings of the endothelium will present as unstable angina (Moise et al 1983). Conversely, plaque rupture is more likely to be the driver of thrombotic occlusion of an artery, which typically leads to an acute myocardial infarction. The gender of the patient may also influence the clinical presentation. The predominant thrombotic trigger in men appears to be plaque rupture, whereas, in women, it is endothelial erosion (Burke AP et al. 1997, Farb et al. 1996). The impact of sex differences on the response to treatment remains a controversial issue.

### *1.2.2 Clinical Presentation and Therapeutic Options*

Thrombosis formation can result in various clinical presentations of ACS: (1) sub-clinical manifestation, (2) unstable angina, (3) non-ST-elevation myocardial infarction (non-Q wave), and (4) ST-elevation myocardial infarction (Q wave), and (5) death. The severity of the presentation depends upon acuteness and degree of obstruction, duration of total occlusion, ability to recruit collateral vessels, and oxygen demands of the myocardium (Ambrose and Weinrauch 1996).

### *Diagnosis*

The traditional approach to the diagnosis of acute coronary syndromes is three fold: (1) assessment of clinical symptoms, (2) electrocardiography on admission, and (3) measurements of biochemical markers (Klootwijk and Hamm 1998).

The first 'red flag' to instigate a clinical investigation is the presence of angina pectoris, which is typically marked by pain and tightness of the chest. There are several degrees of severity and duration of chest pain.



Thus, in attempts to rank patients according to the severity of angina several classification systems have been developed: the Braunwald Angina Classification (Braunwald 1989, 1994) (Table 1.1); the Canadian Cardiovascular Society (CCS) Angina Classification (Campeau 1976) (Table 1.2); and the New York Heart Association's (NYHA) Functional Classification of Angina Pectoris (Hackett and Cassem 1978) (Table 1.3).

Table 1.1: Braunwald classification for unstable angina.

Severity	
I	Symptoms with exertion beginning in past 2 months.
II	Symptoms at rest in the past month but not for the past 48 hours.
III	Symptoms at rest within the past 48 hours.
Precipitant	
A	Secondary (extrinsic conditions aggravating symptoms)
B	Primary (no contribution of extrinsic conditions)
C	Post-infarction (within 2 weeks of index MI)
Treatment during symptoms	
1	No treatment
2	Usual angina treatment
3	Maximal treatment

Table 1.2 Canadian Cardiovascular Society Angina Classification.

Class I	Ordinary physical activity (such as walking or climbing stairs) does not cause angina. Angina may occur with strenuous, rapid or prolonged exertion (work or recreation).
Class II	There is a slight limitation of ordinary activity. Angina may occur with walking or climbing stairs rapidly; walking uphill; stair climbing after meals or in the cold, in the wind or under emotional stress; walking more than two blocks on the level and climbing one flight of stairs at a normal pace under normal conditions.
Class III	There is a marked limitation of ordinary physical activity. Angina may occur after walking one or two blocks on the level or climbing one flight of stairs in normal conditions at a normal pace.
Class IV	There is an inability to carry on any physical activity without discomfort; angina may be present at rest.



Table 1.3 Functional Classification of Angina Pectoris (NYHA).

Functional Class	Occurrence of Symptoms	Exercise Tolerance (METs)	Functional Impairment
I	With unusual activity	7-8 (or more)	Minimal or none
II	With prolonged or slightly more than usual activity	5-6	Mild (can do light and general industrial work)
III	With usual activity	3-4	Moderate (may be able to do a desk job)
IV	At rest	1-2	Severe (incapacitated)

Also, unstable angina can be classified as primary or secondary. Primary unstable angina is the result of either non-occlusive thrombosis or vasoconstriction (Braunwald 1998). In the majority of the cases, the acute onset of unstable angina is the result of a mural thrombus with approximately 70% occlusion (Ambrose 1992, Patel and Topol 1999). Conversely, secondary angina is caused by tachycardia in conjunction with coronary stenosis or chronic stable angina, which results in a greater demand for oxygen by the myocardium (Braunwald 1998).

Each classification system has their strengths and limitations, and is subject to observer bias. As a result the use of these classification systems alone in the risk stratification of patients is not likely to be sufficient.

### *Electrocardiography and Imaging Technology*

An electrocardiogram (ECG) upon admission will measure any deviations from the normal heart rhythm. This diagnostic tool provides objective diagnostic information in addition to clinical symptoms. When a myocardial infarction (MI) results in a downturn in the ST- and T-waves, the event is classified as a ST-segment depression MI (non-Q-wave). This event differs from unstable angina such that the vessel becomes temporarily occluded (i.e., <1 hour) and relatively mild myocardial necrosis occurs during a non-



ST-segment elevation myocardial infarction. A ST-segment elevation (Q-wave) MI is substantially more severe than the previously described events. In this case, the vessel is completely occluded for a substantial period of time (i.e., >1 hour) leading to severe myocardial damage (Fuster et al 1992).

In addition to changes in the heart rhythm, clinicians are also interested in the state of the coronary anatomy. Coronary angiography has been established as the gold standard in the evaluation of the coronary anatomy. This technique uses radiographic imaging technology to inspect the coronary circulation in multiple projected longitudinal planes by comparing 'diseased' segments to 'normal' segments (Topol 1998). Angiograms offer valuable insight into the arterial lumen but fall short, as it does not reveal unstable micro-plaques or the progression of stable plaques (Fuster et al 1999). Recent advances in diagnostic tools such as intravascular ultrasound (IVUS), electron-beam tomography and angioscopy may provide possible solutions to this problem (Fuster et al 1999). The capabilities of magnetic resonance imaging (MRI) also show promise in the animal model as a tool to identify unstable coronary plaques (Fayad et al. 1998).

### *Biomarkers*

As the understanding in the pathophysiology of acute coronary syndromes is expanding, so too is the importance of biochemical markers in the early assessment of these patients. Most of these markers are generated during the inflammatory response to plaque rupture and muscle damage. Cardiologists pay special attention to levels of several enzymes such as creatine kinase (CK), creatine kinase myocardial band (CK-MB) isoenzyme, troponin I (TnI) and troponin T (TnT), and C-reactive protein (CRP) (Ohman et al 1996, Antman et al 1996, Tardiff et al 1999, Giannitsis





et al 2000, Heeschen et al 2000). CK and CK-MB are released when muscle is damaged. These biomarkers however, are relatively insensitive when mild myocardial necrosis occurs as a result of a transient occlusion of a vessel. Patients suffering from non-Q-wave (non-ST-segment elevation) myocardial infarctions tend to have an associated increase of twice over the upper limit of normal level of CK. When levels do not or only slightly extend past normal, those patients are usually classified as having unstable angina (Klootwijk and Hamm 1999).

The importance of troponins I and T has only been realized within the past 10 years. These markers are expressed only in cardiac myocytes and are in low levels in the plasma of healthy individuals (Klootwijk and Hamm 1999). Upon destruction of myocardium, high levels of troponins are released into the circulation and are detectable at even low level of myocardial damage (Heeschen et al 2000). In the clinical setting, the Global Utilization of Strategies to Open Occluded Coronary Arteries (GUSTO) IIA investigators found that a single measurement of troponin T two hours after admission was highly predictive of 30-day mortality and other major complications (Ohman et al 1996). Troponin I follows a similar relationship (Antman et al 1996). These results suggest that troponin T and I may significantly improve upon the diagnostic information provided by biomarkers already available due to their sensitivity of myocardial damage (Hamm 2001).

C-reactive protein (CRP) is one of the most recent biomarkers under investigation. This protein is released as part of the inflammatory response and is thought to contribute to plaque disruption. As intuitive as the association seems, the body of evidence is mixed. In one study of angina patients, those with the unstable condition had higher levels of CRP than did those with stable angina (Haverkate et al 1997). Yet, the CAPTURE



investigators found that CRP was not predictive of cardiac risk in unstable angina patients (Heeschen et al 2000). Until more clinical investigations are reported, the predictive power of CRP will remain uncertain.

### *Treatment Strategies*

#### *Medical Management*

Medical management of acute coronary syndromes is a non-invasive attempt to control the symptoms of ischemia by re-establishing the balance between myocardial oxygen supply and demand. And hence, these efforts are aimed at the prevention of recurrent ischemic events and death, and eliminating the need for revascularization procedures. Traditionally, medical management has been broken into two approaches, anti-ischemic and antithrombotic therapy.

Anti-ischemic therapy has two objectives, (1) to improve patient comfort and (2) to reduce myocardial ischemia. Nitroglycerin is one of the first drugs administered upon admission. It is a short-acting vasodilator, and it reduces the preload and afterload on the heart (Verheugt 1999).  $\beta$ -adrenoceptor blockers act to lower the heart rate and myocardial contractibility, and to control hypertension. Calcium channel antagonists produce similar clinical results to  $\beta$ -blockers, but do not alter the heart rate (Verheugt 1999). For this reason, these agents should be used concomitantly to maximize effectiveness.

Antithrombotic therapy targets the inhibition of clot formation and propagation and thrombolysis. One of the most common anticoagulant agents is heparin. Heparin stimulates antithrombin-III which indirectly inhibits thrombin, a key molecule in the end stages of the coagulation cascade. When administered intravenously, heparin's effects are almost immediate, but effects often vary significantly between patients. For this



reason, low-molecular-weight heparin (LMWH) is often preferred over unfractionated heparin as it is more predictable and it can be administered subcutaneously on an out-patient basis (Verheugt 1999). Hirudin shares the same function as heparin but its mode of attack is directly on thrombin. Like LMWH, hirudin is more predictable than heparin, but has failed to show any incremental benefit of its use over heparin (GUSTO IIb 1996). In addition, the cost of hirudin is prohibitive for its routine use in ACS patients.

Thrombolytic agents (e.g., tissue-plasminogen activator (t-PA) and streptokinase (SK), reteplase, alteplase) may be administered to dismantle the thrombotic occlusion(s) at the root of the myocardial infarction. Specifically, thrombolytic agents are designed to catalyze the cleavage of plasminogen into plasmin at the thrombus site. Activated plasmin then acts to cleave fibrin and hence, degrade the clot.

One of the most effective medical management tools available is the pharmacological inhibition of platelet function. The gold standard is acetylsalicylic acid (aspirin or ASA). Aspirin irreversibly inhibits the cyclooxygenase pathway in platelet, blocks thromboxane  $A_2$  formation and platelet aggregation. Aspirin continually proves to reduce the risk of death and non-fatal MI at both low and high doses. For those patients who cannot tolerate aspirin, a second generation of antiplatelet agents, thienopyridines, may be suitable options. Ticlopidine acts differently than aspirin in that it inhibits ADP receptors on the platelet surface (Theroux and Fuster 1998). This agent binds to the receptors with high affinity, and consequentially, the disappearance of effects takes several days after drug cessation. Unfortunately, ticlopidine has also been associated with higher rates of bleeding compared to aspirin (Theroux and Fuster 1998).





As a result of the rapid evolution in the understanding of platelet physiology in the latter half of the 20<sup>th</sup> century, glycoprotein (GP) IIb/IIIa receptor inhibitors have been named the third generation of anti-platelet agents. Presently, two routes of administration of this class of drugs are available: intravenous and oral. To date, the intravenous drugs, abciximab, eptifibatide and tirofiban, have been extensively studied and are in use in routine clinical practice. Oral GP IIb/IIIa inhibitors (e.g., xemilofiban) are in the early stages of safety and efficacy investigations and await further research and reporting to elucidate their contribution to the treatment of acute coronary syndromes.

The discovery of the GP IIb/IIIa receptor was the culmination of research efforts from several different research areas, including platelet-fibrinogen interactions, Glanzmann thrombasthenia, platelet membrane glycoproteins, integrin receptors, coronary artery pathology and biochemistry, and experimental thrombosis (Coller 1995). Barry S. Coller and his colleagues were the pioneers who realized the vast potential of GP IIb/IIIa receptor blockade with c3E7 Fab in experimental animal models of thrombosis (Coller et al 1985). c3E7 Fab (generic: abciximab; trade name: ReoPro) is a mouse/human chimeric monoclonal antibody fragment that binds to these receptors and inhibits the binding of large ligands. Based on the results of the groundbreaking trial, Evaluation of IIb/IIIa Platelet Receptor Antagonist c7E3 in Preventing Ischemic Complications (EPIC), the Food and Drug Administration (FDA) in the United States approved c3E7 Fab (abciximab, ReoPro<sup>TM</sup>, Eli Lilly/Centocor) for use in high-risk angioplasty and atherectomy on December 22, 1994. Since 1998, two additional agents (i.e., eptifibatide and tirofiban) with a similar target have progressed from the bench to the bedside. Eptifibatide (Integrelin<sup>TM</sup>, COR Therapeutics/Schering-Plough) is a cyclic peptide based on the lysine-glycine-aspartic acid (KGD) sequence found in the snake venom protein



barbourin (Scarborough et al 1991). Similar to eptifibatide, tirofiban's (Aggrastat<sup>TM</sup>, Merck) design is based on a particular amino acid sequence. This peptidomimetic contains the characteristic sequence of arginine-glycine-aspartic acid (RGD) found in most adhesive ligands (Jordan and Mascelli 1999).

Although these intravenous agents share a common goal, they differ by their means to the end. Firstly, these agents do not share a similar size. Abciximab has a molecular weight of 50 kDa, which is significantly larger than eptifibatide (800 Da) and tirofiban (500 Da). This difference dictates the actual binding site on the GP IIb/IIIa receptor. The smaller molecules can easily slide into the fibrinogen-binding dock (KGD and RGD, respectively), whereas abciximab acts as an umbrella by entirely covering the point of entry to the fibrinogen-binding site. Unlike the uni-sequence-specific agents, abciximab also binds to  $\alpha_v\beta_3$  (vitronectin receptor), containing the same  $\beta_3$  subunit as GP IIb/IIIa receptor. The vitronectin receptor mediates cell adhesion, migration, and smooth muscle cell proliferation and thrombin generation (Chronos et al 1999). If abciximab can inhibit these functions, it is hypothesised that it can reduce restenosis after vessel injury (Jordan and Mascelli 1999). In addition, abciximab also binds to the activated MAC-1 receptors on activated leukocytes. MAC-1 receptors can bind to intercellular adhesion molecule-1 (ICAM-1), fibrin(ogen) and factor X (FX). Binding to ICAM-1 results in adhesion of neutrophils and monocytes to the endothelium and sites of fibrin deposition (Chronos et al 1999).

Abciximab also differs from the other inhibitors by its actions in the body. In early studies, a dose-response relationship in the inhibition of platelets was confirmed. As the dose increases so too does the number of receptors occupied, thus, increasing the inhibition of platelet aggregation (Jordan and



Mascelli 1999). Eighty percent occupancy produces an optimal level of anti-platelet aggregation, which in treated patients is achieved with 0.25 mg/kg bolus dose and maintained with a 12-hour infusion at 0.125 ug/kg/min. The stoichiometry is about 1.5 abciximab molecules to each receptor, whereas, both tirofiban and eptifibatide reside on the receptor in a ratio of 100 drug molecules per GP IIb/IIIa receptor (Tcheng 1999).

Table 1.4. Characteristics of GP IIb/IIIa receptor inhibitors.

Characteristic	Abciximab	Eptifibatide	Tirofiban
Type	antibody	peptide	peptidomimetic
Molecular Weight (Da)	~50 000	~800	~500
Binding to Receptor	irreversible	competitive	competitive
Drug to Receptor Ratio	1.5	250-2500	>250
Plasma Half-life (hours)	10-15 mins	2.5	2
50% return of platelet function (without transfusion) (hours)	12	2-4	~4

Da, Daltons

Unbound tirofiban and eptifibatide exit the body via renal clearance in both active forms and as metabolites. These competitive antagonists also share a similar biological half-life of 2 and 2.5 hours, respectively (Tanquay 1999). Conversely, free abciximab is quickly cleared from the plasma with an exceptionally short plasma half-life of 10 to 15 minutes. The biological half-life however, is much longer due to abciximab's high affinity for the GP IIb/IIIa receptor (Jordan et al 1996). It is not until 4 to 6 hours after the initial bolus that partial function of the platelet can be recovered (Mascelli et al 1998). Even after 24 hours, receptor blockade remains between 50% and 60%. This gradual recovery of function is unique to abciximab and is thought to be the root of its long lasting effectiveness. However, the inability of abciximab to readily disengage from the receptors can also pose a danger to patients in the form of major bleeding. With the cessation of eptifibatide or tirofiban, these drugs quickly lose affinity for the receptors and platelet function can be restored to minimize bleeding complications.



Percutaneous coronary intervention (PCI) can result in the disruption or dissection of the arterial wall, which leads to platelet activation and thrombosis. Seemingly, the attributes of these agents would be able to contribute to the reduction of these complications. Because thrombosis is a key factor in ischemic complications associated with this treatment, massive efforts have been put towards assessing the efficacy of GP IIb/IIIa inhibitors in PCI patients (Azar et al 1997). In following chapter, a review of these efforts is presented.

### *Coronary Interventions*

The late 1960s and 70s marked the era of revascularization with the advent of coronary artery bypass graft surgery (CABG) and percutaneous coronary interventions (PCI), respectively (Favaloro et al 1969, Gruntzig et al 1979). Overall, these are mechanical techniques to restore perfusion to jeopardized myocardium. The CABG surgery involves the grafting portions of either the saphenous vein or the internal mammary artery to bypass obstructed coronary arteries (Dorland 1994). Percutaneous transluminal coronary angioplasty (PTCA) is a seemingly less invasive procedure whereby a balloon catheter is inserted into the femoral or brachial artery and travels via the lumen of the vessel to the lesion site where the balloon is inflated to flatten the plaque against the artery wall (Dorland 1994). Since the introduction of these techniques, numerous studies have tried to quantify and compare their effects in relation to each other or in conjunction with other therapeutic options (Moliterno and Elliot 1995). In the early studies, no significant long-term difference in mortality rates was observed. However, repeat revascularization procedures were more frequent in angioplasty patients. Often these studies have grouped patients based on the number of disease vessels, but another important factor, the location of the lesion with respect to other vessels and within the vessel





itself was not taken into account. These features of the coronary anatomy were however taken into account in a recent population-based investigation (Hannan et al 1999). From January 1993 to December 1995, data from nearly 60 000 patients enrolled in the New York State cardiac procedures registry were used to estimate the three-year survival rate in patients who had undergone CABG or PTCA. Overall, the three-year survival rate in CABG patients was 91.4% and in PTCA patients, 94.6%. These results must also be taken under caution. When broken down by lesion severity location, patients who had greater lesion complexity and underwent CABG had statistically significant higher survival rates. PTCA provided better survival outcomes to those with single-vessel and no involvement of the left anterior descending artery. It seems that the survival benefits are strongly predicted by the extent and location of the lesion. Thus, angioplasty is most often reserved for patients with single-vessel disease or easily accessible multi-vessel disease, whereas, patients with severe multi-vessel or failed angioplasty are more likely to receive CABG.

Unfortunately, one of the major limitations of angioplasty has been restenosis, which occurs in about 50% of patients, and the need for repeat target-vessel revascularization in 20% of patients (Stone 1998). With the goal of minimizing these complications, a promising new device called a stent was introduced in the 1980s. A stent is an endovascular scaffolding device implanted in the target vessel and was designed to increase its structural integrity. The BENESTENT and STRESS trials were the two landmark trials to reveal its potential (Serruys et al 1994, Fischman et al 1994). To confirm the short- and long-term benefits of stenting, a study by Hannon et al (2000) compared outcomes for stent placement and single-vessel balloon angioplasty in a large cohort of almost 20 000 patients. Overall, stent placement was related to significantly lower risk-adjusted long-term mortality, CABG and repeat PCI rates as compared with balloon



angioplasty. As with any device, the risk of complications does exist. Stent implantation can activate the expression of GP IIb/IIIa receptors on the platelet surface and predisposes the coronary artery to thrombosis. The use of a metal prosthetic device during the procedure may lead to thrombus inside the stent, embolization of atherosclerotic material or thrombus, and cause side branch closures in some patient when a branch becomes trapped. Fortunately, most of these triggers can be controlled by GP IIb/IIIa inhibition (EPISTENT 1998).

#### *New Frontiers: Facilitated PCI*

A novel technique dubbed as facilitated percutaneous coronary intervention, is emerging with promise to meld the best of fibrinolysis, GP IIb/IIIa receptor blockade and angioplasty (and stent implantation). Facilitated PCI is an assortment of different therapeutic approaches whose aim is to use medical management to improve the outcomes of those undergoing early percutaneous coronary intervention for acute myocardial infarction. Such combinations include the following: fibrinolysis with early PCI, rescue PCI after failed fibrinolysis, primary PCI with adjunctive GP IIb/IIIa inhibitors, or combination therapy with fibrinolytics, GP IIb/IIIa inhibitors and PCI (Li and Herrmann 2000). The latter is the most comprehensive approach taken with acute myocardial infarction patients. Two trials have been designed to assess this new approach. The Strategies for Patency Enhancement in the Emergency Department (SPEED-GUSTO IV) trial is a pilot trial of the larger GUSTO-IV trial. The SPEED trial was designed to assess the safety and efficacy of various doses of reteplase with abciximab in patients with ST-segment elevation. In these patients, early PCI was encouraged and angiographic data were collected for all treatment groups. Preliminary results suggest that patients undergoing early PCI and receiving full-dose abciximab and reduced-dose reteplase experienced lower re-occlusion rates and PCIs were more likely



to be successful (Califf 1999 and SPEED Group 2000). The second trial, the Thrombosis In Myocardial Infarction-14 (TIMI-14) trial, examined patients with ST-segment elevation who underwent early PCI. In patients who received low-dose alteplase and abciximab, there was a higher rate of ST-segment resolution compared to those who had received only fibrinolytics (de Lemos et al 2000). Overall, these are promising results for an emerging new approach to the treatment of myocardial infarction.





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# CHAPTER 2: LITERATURE REVIEW

## 2.1 INTRODUCTION

An impressive number of trials have been designed to investigate the effects of GP IIb/IIIa inhibitors in patients with acute coronary syndromes, both alone or in combination with other pharmacological agents and/or coronary interventions (Table 2.1). This literature review will examine the body of evidence generated from the clinical trials of the three intravenous GP IIb/IIIa inhibitors, abciximab, eptifibatide, and tirofiban, with particular focus on their utilization and outcomes in PCI patients. To further define the selection of this evidence, only single- or multi-centred, randomized, placebo-controlled clinical trials were considered for the following outcomes: all-cause mortality, repeat revascularization (e.g., PCI or CABG) and quality of life measured at various points in time (e.g., 30 days, 6 months, 1 year after randomization). Complications and subgroups analyses (e.g., diabetic patients) will also be briefly discussed.

Table 2.1: Clinical Trials of Abciximab (Abx), Eptifibatide (Ept) and Tirofiban (Tiro).

<i>Trial Name</i>	<i>Interventions</i>
ASSENT-3 (Assessment of the Safety and Efficacy of a New Thrombolytic-3)	TNK-tPA+enoxaparin TNK-tPA+Abx
CACHET (Comparison of Abciximab Complications with Hirulog (and backup Abciximab) Events Trial)	Abx+aspirin+WA-heparin Bivalirudin+aspirin+Abx
CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications)	PTCA PTCA+Abx Stent Stent+Abx
CAPTURE (C7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina)	PCI+Abx PCI+Placebo
EPIC (Evaluation of c7E3 for the Prevention of Ischemic Complications)	PCI+Abx bolus PCI+Abx bolus+infusion PCI+Placebo





<i>Trial Name</i>	<i>Interventions</i>
EPILOG (Evaluation of PTCA to Improve Long-term Outcome by cF7E3 Glycoprotein receptor blockade)	PCI+Abx+low dose heparin PCI+Abx+standard dose hep.
EPISTENT (Evaluation of IIb/IIIa Platelet Inhibitor for STENTing)	PCI+placebo Stent+Abx Stent+Placebo PTCA+Abx
ERASER (Evaluation of ReoPro and Stenting to Eliminate Restenosis)	Stent+Abx 12hr infusion Stent+Abx 24hr infusion Stent+Placebo
GUSTO IV ACS (GUSTO IV Acute Coronary Syndromes)	Abx bolus+24hr infusion Abx bolus+48hr infusion Placebo
GUSTO IV AMI (GUSTO IV Acute Myocardial Infarction)	Full-dose Reteplase+ASA+Heparin Half-dose Reteplase +Abx+ASA+Heparin
GUSTO-IV-SPEED (Strategies for Patency Enhancement In the Emergency Department)	Abx
ISAR-2 (Intracoronary Stenting and Antithrombotic Regimen-2)	Abx+Reteplase Abx bolus+infus+heparin 12hr Intra-arterial heparin
ORBIT (Oral glycoprotein IIb/IIIa Receptor Blockade to Inhibit Thrombosis)	Two doses xemilofiban after Abx+PTCA Placebo after Abx+PTCA
RAPPORT (ReoPro in Acute myocardial infarction and Primary PTCA Organization and Randomized Trial)	PTCA+Abx PTCA+Placebo
STOP-AMI (Stent vs Thrombolysis for Occluded coronary arteries in Patients with Acute Myocardial Infarction)	Abx+Stent Alteplase
TIMI-14 (Thrombolysis in Myocardial Infarction)-14	t-PA Abx+t-PA Abx+SK Abx
ESPRIT (Enhanced Suppression of Platelet Receptor GP IIb/IIIa using Integrilin Therapy)	PCI+Ept PCI+Placebo
IMPACT-II (Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-II)	PCI + Ept bolus+ low-dose infus PCI+ Ept bolus+ high-dose infus PCI+ Placebo bolus+infus
PURSUIT (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression using Integrilin Therapy)	Ept Placebo



<i>Trial Name</i>	<i>Interventions</i>
AtoZ (Aggrastat to Zocor)	Tiro Simvastatin
PRISM (Platelet Receptor Inhibition for Ischemic Syndrome Management)	Tiro Heparin
PRISM-PLUS (PRISM-in Patients Limited to Very Unstable Signs and Symptoms)	Tiro+Heparin Heparin
RESTORE (Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis)	PCI+Tiro PCI+Placebo
TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy)	Tiro Conservative vs Invasive Treatment
TARGET (do Tirofiban And ReoPro Give similar Efficacy outcomes Trial?)	Tiro Abx
PRICE (Prairie ReoPro versus Integrilin Cost Evaluation)	Ept Abx

Abx, Abciximab; ASA, acetylsalicylic acid (aspirin); Ept, Eptifibatide; infus, infusion; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; SK, streptokinase; Tiro, Tirofiban; t-PA, t-plasminogen activator.

## 2.2 UTILIZATION OF GP IIb/IIIa INHIBITORS

Tremendous effort has gone and continues to go into defining the effects of GP IIb/IIIa inhibitors in the clinical trial setting (Table 2.2). Yet, compared to the abundant amount of published literature on the results of these clinical trials, the reports on utilization in current practice are quite sparse.

Of the handful of published observational utilization studies of GP IIb/IIIa inhibitors, abciximab was most often characterized. Abciximab was the first to be approved by the FDA (in 1994) and was introduced to clinical practice in 1996 or 1997 (Weiss et al 1999, Millhouse and Shaw 2000, Paradiso-Hardy et al 1999). In Alberta, the use abciximab was launched in July 1997 (D. Daniec, Personal communication).

Several points that should be considered when describing the utilization of these therapies: temporal trends/changes; inter-institutional differences;



and the characteristics of patients receiving this therapy. Researchers at the Seton Medical Centre in San Francisco investigated patients who had undergone PCI between 1997 and 1999 for temporal trends or changes in their use of GP IIb/IIIa inhibitors (Millhouse and Shaw 2000). Abciximab was first agent available and was used in 27% of all PCIs in 1997. By the first quarter of 1999, more than 70% of the PCI patients received a GP IIb/IIIa inhibitor (either abciximab or eptifibatide). In the second quarter of 1999, 92.0% of the patients who had received GP IIb/IIIa inhibitors received eptifibatide. The considerably lower cost of eptifibatide (compared to abciximab) may be the cause for the dramatic switch to eptifibatide from abciximab.

Inter-institutional differences in the utilization of GP IIb/IIIa inhibitors have also been assessed. Paradiso-Hardy and colleagues (1999) sought to describe the utilization of abciximab from October 1, 1996 to March 31, 1997 in Canadian interventional cardiology centres. This retrospective descriptive study surveyed all 34 interventional cardiology centres using a standardized questionnaire. In their preliminary analysis they found that the utilization of abciximab varied significantly both between and within provinces across Canada. Inter-institutional differences were also discovered in a study of 5113 consecutive PCI procedures from six American hospitals, where the use of abciximab ranged from 14% to 42% (O'Donnell et al 1999).

The characteristics of recipients of GP IIb/IIIa inhibitors are also important. Weiss et al (1999) retrospectively collected medical resource utilization data on 1259 patients undergoing PTCA between January 1, 1996 and June 15, 1997 in eight teaching hospitals in the United States. They found that abciximab was administered to 45% of all patients, and 54% of those were undergoing urgent PTCA and 40% of those were undergoing elective



PTCA. In terms of clinical indications for its use, abciximab was used in 57% of patients with recent myocardial infarctions, 42% with uncomplicated angina, and 38% with positive stress tests (Weiss et al 1999). In general, 84% of these patients received abciximab because they were deemed high risk, and 16% of patients received this agent for 'bail out' procedures.

The implications of utilization patterns span from the patient level to the policy level. Clinicians, for instance, may be interested in tracking the performance of patients who receive GP IIb/IIIa inhibitors in relation to those who do not receive these agents. Based on those results, practice may be altered to maximize the benefits to patients. Policy makers and those in charge of health resource funding may find utilization data helpful in projecting future demand for associated resources.

### 2.3 ABCIXIMAB

Four randomized, placebo-controlled clinical trials define the early knowledge regarding the role of abciximab as an adjunctive therapy to PCI. These include the EPIC, EPILOG, CAPTURE, and EPISTENT trials (Table 2.2). In addition, several emerging trials have been designed to deal with issues uncovered in earlier trials and to reflect the current milieu of treatment of ACS (e.g., RAPPORT, ERASER, CADILLAC). In most cases, the results from these trials are still pending.





Table 2.2. Clinical trials of abciximab and PCI.

Authors	Patients	Interventions	Outcomes	Results
EPIC Investigators	N=2099 high-risk (rescue and direct) PCI patients, all treated with ASA & heparin, between November 1991 and November 1992.	1. Placebo (n=696) (Ref.) 2. Abx+placebo infusion (n=695) 3. Abx+ Abx infusion (n=708)	Composite endpoint: 1) All-cause mortality 2) MI 3) Urgent revasc. At 30, 180 days and 3 years.	Composite endpoint: 30 days: Abx+placebo inf: (placebo vs Abx) 12.8% vs 11.5% RRR=10% p=0.43 Abx+Abx inf: 12.8% vs 8.3% RRR=35% p0.008 180 days: Abx+Abx inf: 35.1% vs 27.0% RRR=23%p=0.001. 3 years: Abx+ Abx inf: 47.2% vs 41.1% RRR=13%p<0.01.
EPILOG	N= 2792 all treated with ASA, underwent elective or urgent PCI between February 1995 and December 1995.	1. Placebo+ std. heparin (n=939) (Ref) 2. Abx+ std. heparin (n=918) 3. Abx+low-dose heparin (n=935)	Composite endpoint: 1) All-cause mortality 2) MI 3) Urgent revasc. At 30 and 180 days.	Composite endpoint: 30 days: low-dose: 11.7% vs 5.2% RRR=56% p<0.001 std. dose: 11.7% vs 5.4% RRR=54% p<0.001 180 days: low dose: 14.7% vs 8.4% RRR=43% p>0.05 std dose: 14.7% vs 8.3% RRR=44% p<0.05
EPISTENT Investigators	N=2399 underwent urgent or elective PCI with stent, all treated with ASA & heparin between July 1996 and September 1997.	1. Stent + Placebo (n=809) (Ref) 2. Stent+Abx (n=794) 3. Balloon angioplasty +Abx (n=796)	Composite endpoint: 1) All-cause mortality 2) MI 3) Urgent revasc. At 30 days.	Composite endpoint: 30 days: Stent+ Abx HR=0.48 p<0.001 Angiopl+ Abx HR=0.63 p<0.01
CAPTURE Investigators	N=1265 high risk UA, underwent PCI, all treated with ASA and heparin between May 1993 and December 1995.	1. Placebo (n=635) (Ref) 2. Abx (n=630)	Composite endpoint: 1) All-cause mortality 2) MI 3) Urgent revasc. At 30 and 180 days.	Composite endpoint: 30 days: 15.9% vs 11.3% RRR=29% p<0.05 180 days: 30.8% vs 31.0% RR=1.00 NS.



Authors	Patients	Interventions	Outcomes	Results
ERASER Investigators	N=225 underwent stent implantation, all treated with ASA & heparin between May 1996 and February 1997.	1. Placebo (n=71) (Ref) 2. Abx 12 hr infusion (n=79) 3. Abx 24 hr infusion (n=75)	Composite endpoint: 1) All-cause mortality (in-hospital) 2) MI 3) Revasc. At in-hospital and 180 days.	Composite endpoint: In-hospital: Both with p>0.05 180 days: Both with p>0.05.
RAPPORT Investigators	N=483 with ST-segment elevation MI, underwent PCI between November 1995 and February 1997	1. Placebo (n=242) (Ref) 2. Abx (n=241)	Composite endpoint: 1) All-cause mortality 2) Re-MI 3) Urgent revasc. At 30 and 180 days.	Composite endpoint: 30 days: OR=0.49 p<0.05 180 days: OR=0.61 p<0.05.
CADILLAC Investigators	N=2082 with AMI (time period to be announced).	1. PTCA alone (n=516) (Ref) 2. PTCA+Abx (n=529) 3. Stent alone (n=512) 4. Stent + Abx (n=525)	Primary endpoint: 1) All-cause mortality At 180 days.	Endpoint: 180 days: Preliminary results: No significance difference between groups.
ADMIRAL (Barragan et al)	N=300 with AMI (time period to be announced).	1. Placebo + stent (n=151) (Ref) 2. Abx + Stent (n=149)	Primary endpoint 1) All-cause mortality 2) Re-MI 3) Urgent revasc. Secondary endpoint 1) All-cause mortality 2) Re-MI 3) Any revasc. At 30, 180 days.	Endpoint: 30 days: Primary: 14.7% vs 7.3% RRR=50% p<0.05 Secondary: 21.3% vs 13.3% RRR=38% p<0.05 180 days: Primary: 16.0% vs 8.0% RRR=50% p<0.05 Secondary: 34.7% vs 23.3% RRR=11% p<0.05

Infus, infusion; HR, hazard ratio; MI, myocardial infarction; OR, odds ratio; Ref, reference group; RRR, relative risk reduction; revasc., revascularization; vs=versus.

### *EPIC Trial*

Abciximab was the first GP IIb/IIIa receptor inhibitor to be tested in a large-scale, randomized placebo-controlled trial called the Evaluation of c7E3 in Preventing Ischemic Complications (EPIC) trial (1994). The investigators focused on the assessment of efficacy of abciximab at 30 days and six months in patients who were at high-risk for complications after balloon angioplasty or directional atherectomy. In terms of treatment dosages



selected, the comparison of the single bolus to the bolus-plus-infusion treatment allowed for the evaluation of a gradient effect. And finally, the investigators assessed the safety of concomitant abciximab with aspirin and heparin. Those patients who qualified were enrolled and randomized to one of three treatment groups:

- Abciximab 0.25 ug/kg bolus plus placebo infusion (n=695)
- Abciximab 0.25 ug/kg bolus plus 10 ug/kg/min infusion for 12 hours (n=708)
- Placebo bolus plus placebo infusion (n=696)

All 2099 patients were given aspirin, and heparin therapy lasted until after completion of the intervention. Sheathes were removed on the day after the intervention. (A sheath is a tubular case or envelop implanted at the access site (i.e., femoral or brachial artery) of the catheter). The primary efficacy endpoint included all-cause death, myocardial infarction, revascularization (e.g., urgent PTCA or CABG), and failure of index PTCA requiring stent or intra-aortic balloon pump (IABP) placement.

The importance of this trial was captured in the striking reduction of 35.2% in the primary endpoint at 30 days for placebo versus abciximab bolus plus infusion (12.8% vs 8.3%, p-value=0.008). Among patients followed for 6 months, the abciximab-treated patients experienced a 23.0% relative risk reduction in the primary composite endpoint (Topol et al 1994). Even after 3 years of the initial intervention, the beneficial effects of abciximab persisted (relative risk reduction of 13%). Never before had a pharmacological intervention make such an impact on the outcomes of a mechanical intervention. This exciting result was the catalyst for subsequent trials of GP IIb/IIIa inhibitors.



Unfortunately, this good news was also accompanied by a doubling of red blood cell and platelet transfusions and major bleeding (as defined by the TIMI scale (Rao et al 1988)) (Aguirre et al 1995).

Overall, three conclusions can be drawn from the EPIC trial. Firstly, the use of abciximab as an adjunct to PCI significantly lowered death, myocardial infarction, and revascularization at 30 days and 6 months. Secondly, the best outcomes were seen in the bolus plus infusion treatment arm. To maintain clinical effectiveness, the 12-hour infusion was necessary. And lastly, safety concerns (e.g., bleeding complications) were brought to light as an area for improvement and refinement in following trials.

### *EPILOG Trial*

On the heels of the EPIC trial, a pilot study was conducted by Lincoff et al (1997) to address the safety concerns revealed in EPIC. In this investigation, they revealed that low-dose weight-adjusted heparin reduced bleeding complications found in patients who received the standard dose. Based on these results, the Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade (EPILOG) trial was constructed to assess this new information on a larger scale. Two points were addressed in this trial. Firstly, the investigators wanted to see if abciximab's effect was beneficial to patients of all risk levels undergoing percutaneous coronary intervention. Secondly, low-dose heparin would be used in hopes of reducing the incidence of bleeding complications found in the EPIC trial.

This double-blind, randomized, placebo-controlled trial enrolled 2792 patients from 69 sites across the United States and Canada (EPILOG Investigators 1997) who were undergoing elective or urgent percutaneous revascularization with angioplasty (95%) or directional coronary





atherectomy (5%). Participants were randomly assigned to one of three treatment arms:

- Abciximab 0.25 ug/kg bolus plus 0.125 ug/kg/min infusion for 12 hours; standard heparin dose 100U/kg bolus plus additional boluses to achieve activated clotting time (ACT) of 300 seconds. (n=918)
- Abciximab 0.25 ug/kg bolus plus 0.125 ug/kg/min infusion for 12 hours; low-dose heparin 70 U/kg bolus plus additional boluses to achieve ACT of 200 seconds (n=935).
- Placebo plus standard-dose heparin (n=939).

Aspirin was administered to all patients. And heparin was terminated immediately after the procedure was completed, and sheaths were removed when activated clotting time (ACT) reached 175 seconds or less. Stent implantation was discouraged and reserved for situations of threatening or actual abrupt vessel closure.

The primary efficacy endpoint was a composite of all-cause death, myocardial infarction or re-infarction, and revascularization (e.g., repeat angioplasty or CABG) at 30 days. This same endpoint was evaluated again at 6 months. As in EPIC, major bleeding, transfusions and thrombocytopenia were assessed.

The initial design of the trial suggested a sample size of 4800 patients, however, the interim analysis on 2792 patients provided overwhelming evidence of abciximab's beneficial effects. And hence, enrolment ceased. At 30 days, both abciximab-treated patients yielded a 55.6% (low-dose heparin) and 53.8% (standard dose heparin) risk reduction in the primary composite endpoint when compared to the placebo treatment (p-values <0.001, <0.001, respectively). Similarly, the investigators reported dramatic reductions in the individual components of the composite



endpoint. Between the abciximab treatments, either heparin regimen produced comparable results in all patient groups. In terms of bleeding complications, incidences of major bleeding, red blood cell and platelet transfusion and intra-cranial haemorrhage (or stroke) were not significantly different between the groups. However, minor bleeding was more common in the abciximab-standard-dose-heparin group ( $p\text{-value}<0.001$ ).

One of the aims of this trial was to examine abciximab's effect in patients of all risk levels. When the population was broken down into high and low-risk strata, both groups of patients benefited from the study drug. Other subgroup analyses included age, gender, and weight, and overall, the benefit of abciximab was homogenous in these subgroups.

At six months, abciximab continued to be effective in reducing the primary composite endpoint when compared to the placebo group (relative risk reductions: 42.9% in abciximab-low-dose heparin, 43.5% in abciximab-standard-dose heparin,  $p\text{-values}=<0.001$ ,  $<0.001$ , respectively). However, when including the rates of *any* revascularization in the composite measure, there is little difference between the treatments (25.8% placebo, 22.8% abciximab + low-dose heparin ( $p\text{-value}=0.07$ ), 22.3% abciximab + standard-dose heparin ( $p\text{-value}=0.04$ ). Among the individual endpoints, risk reductions in the rates of non-Q-wave myocardial infarction and urgent revascularization were still significant at six months, but the rate of non-urgent revascularization was actually higher in the patients treated with abciximab. Inclusion of all revascularization procedures seemed to be the source of the attenuated effect in the overall composite endpoint at six months.

A paper published in 1999 reported the outcomes at one-year for the EPILOG participants (Lincoff et al 1999). In comparison to the placebo



group, the abciximab-treated patients experienced a relative risk reduction of 40.4% and 41.0% in the composite endpoint (p-values<0.001, <0.001, respectively). Again, the types and circumstances of the revascularization included in the composite endpoint had an impact. As was shown at 30 days, when all revascularizations were accounted for the treatment effect of abciximab was lost. It seemed that abciximab's effect was significant only in those who underwent urgent revascularization (p-value<0.005).

Several inferences can be drawn from the results of this trial. Firstly, the addition of abciximab to non-urgent, elective coronary intervention seemed to significantly reduce the rates of adverse clinical events in patients across all risk strata. This trial also contributes by confirming the results of the EPIC trial (EPIC Investigators, 1994) in both the short- and long-term. Although no difference in efficacy between the two abciximab treatment arms was evident, minor bleeding complications were reduced in the low-dose heparin group, which support the findings of the preceding pilot study (Lincoff et al, 1997). There are two caveats of this and the EPIC trial. Firstly, the impact of abciximab in conjunction with routine stent implantation and rotational atherectomy was not examined. And secondly, the use of abciximab as a 'rescue' therapy during coronary intervention was not addressed in the above trials. This treatment strategy is frequently used if a patient is at a risk of possible or actual complications due to the PCI procedure (Tcheng 1996). These 'knowledge gaps' prompted the next series of investigations to capture the effect of abciximab in the contemporary setting of interventional cardiology.

### *CAPTURE Trial*

From 1993 to 1995, 1265 patients who were high-risk acute refractory unstable angina (Braunwald Class III) and had a culprit lesion suitable for balloon angioplasty were enrolled into the c7E3 Fab AntiPlatelet Therapy in



Unstable REfractory angina (CAPTURE) trial (CAPTURE Investigators, 1997). This trial has two unique features; (1) enrolled patients had refractory unstable angina, and (2) abciximab was administered 18 to 24 hours before and one hour after angioplasty, rather than only administration during and after the procedure. These patients, from 69 sites in 12 countries, received the standard regimen of aspirin and heparin. Heparin was administered from before randomization until 1 hour after angioplasty, and adjusted to reach an anticoagulation target of 300 seconds. Within two hours of randomization, patients began one of the two treatments:

- Abciximab 0.25 ug/kg bolus plus abciximab 10 ug/kg/min infusion (n=630)
- Placebo bolus and placebo infusion (n=635)

In contrast with other studies, the patients in CAPTURE were pre-treated with the study drugs 18 to 24 hours before angioplasty and for 1 hour after the procedure. Stent implantation was not encouraged but could be used if an abrupt vessel closure was pending. Sheaths remained in place until 4 to 6 hours after the discontinuation of heparin and the study treatment.

The primary efficacy endpoint was a composite of the incidence of all-cause death, myocardial infarction, or urgent revascularization (e.g., repeat angioplasty, CABG, intra-coronary stent placement, or intra-aortic balloon pump). Bleeding complications were also assessed according the TIMI classification.

At 30 days, the incidence of the primary composite endpoint was reduced by 28.9% in the abciximab-treated group compared to the placebo group (11.3% vs 15.9%, respectively, p-value=0.012). The majority of this reduction can be account for by the individual measure of myocardial





infarctions. The rate of myocardial infarction dropped by 46.7% between these two groups ( $p$ -value=0.003). Even though the occurrence of myocardial infarction before angioplasty was rare, the most dramatic risk reduction was observed before and during the coronary intervention (71.4% (before) and 52.7% (during)). The efficacy endpoints were also re-evaluated at 6 months. Unlike the earlier trials, the composite endpoint or its individual components were not significantly different between the groups. This is not surprising as these patients were treated with the study drug 18 to 24 hours before the procedure and for only 1 hour afterwards. Intuitively, optimal platelet function inhibition could not be sustained after the procedure, especially in the long-term (e.g., six months). According to the investigators, similar results were observed in all subgroups and were independent of age, gender, ECG findings at enrolment, and the presence of diabetes, peripheral vascular disease or renal dysfunction (EPILOG Investigators 1997).

In general, major bleeding was infrequent and happened in only 3.8% of the study population. However, in those who did experience this complication the incidences of major and minor bleeding and transfusions were significantly lower in the placebo group at 30 days (50.0%, 58.3%, 52.1%, respectively;  $p$ -value<0.05 for all).

Combined experience of the EPIC, EPILOG, and CAPTURE trials characterized the role of GP IIb/IIIa inhibition in the early years of percutaneous coronary intervention. Overall, death, myocardial infarction and revascularization rates were drastically reduced in patients who underwent PCI and received abciximab. However, the clinical community remained somewhat apprehensive about bleeding complications and restenosis.



### *EPISTENT Trial*

Two groundbreaking studies published in 1994 gave a boost to the use of stent implantation in the treatment of coronary artery disease (Serruys et al 1994, Fischman et al 1994). They revealed that coronary stent implantation effectively decreases the rate of abrupt vessel closure and restenosis after percutaneous coronary intervention. However, the EPIC, EPILOG and CAPTURE trials had all discouraged the use of stents, unless required for actual or threatening abrupt vessel closure. In an attempt to define the relationship between stent implantation and abciximab, the Evaluation of Platelet GP IIb/IIIa Inhibitor for STENTing (EPISTENT) trial was assembled (EPISTENT Investigators 1998).

In 63 centres in the United States and Canada, 2399 patients who were scheduled for elective or urgent PCI (e.g., balloon angioplasty) were enrolled in this randomized placebo-controlled double-blinded trial. Aspirin and heparin was administered to all patients, and ticlopidine was given at the discretion of the physician. Patients were then randomly allocated to one of three treatment arms:

- Balloon angioplasty plus abciximab 0.25 ug/kg bolus plus 0.125 ug/kg/min infusion for 12 hours (n=796)
- Stent plus abciximab 0.25 ug/kg bolus plus 0.125 ug/kg/min infusion for 12 hours (n=794)
- Stent plus placebo (n=809)

The EPISTENT investigators recommended the Johnson and Johnson Palmaz-Schatz stent, a validated 1<sup>st</sup>-generation stent but other stents were permitted if this kind of stent was not appropriate.

The primary efficacy endpoint of the trial was the combination of death, myocardial infarction or re-infarction, urgent revascularization (e.g., PTCA, CABG) within 30 days. Secondary endpoints combined death or



myocardial infarction (Q-wave or large non-Q-wave). Bleeding complications were also assessed.

At 30 days, those patients who underwent both stent implantation and abciximab treatment experienced the greatest benefit in the reduction of the primary endpoint (5.3% with stent + abciximab treatment compared with 10.8% in the stent alone group, relative risk reduction of 50.9%, (p-value<0.001) and compared with 6.9% in the balloon angioplasty + abciximab group, relative risk reduction of 36.1% (p-value=0.007)). Unlike previously described trials, the inclusion of *any* revascularization in the composite endpoint did not significantly reduce the beneficial effect of abciximab and stent implantation compared to the placebo. When only death or large myocardial infarction (>5 times upper normal limit of CK) were considered, again, the stent plus abciximab group had the advantage (3.0% stent + abciximab vs 7.8% stent + placebo (p-value=0.010), 4.7% balloon + abciximab vs 7.8% stent + placebo (p-value<0.001)). Bleeding complications were rare and homogenous among the treatment groups. These benefits were found consistently across age, gender, weight, and presence of diabetes and clinical indications. However, in terms of intervention, women fared better when undergoing balloon angioplasty. The investigators attribute this finding to incompatibility of the stent (e.g., size) to the more narrow coronary arteries in women (EPISTENT Investigators 1998).

Upon follow-up at one year, the incidence of death, myocardial infarction or any revascularization was reduced by 16.3% in patients undergoing stent implantation and abciximab compared to the placebo group (p-value=0.039) (Topol et al 1999). The most remarkable results were found in the individual endpoints of death and myocardial infarctions (58.3%, p-value=0.037; 47.8%, p-value<0.001, respectively). Target revascularization



rate at one year, however, was not significantly different between the three groups.

Diabetes is a strongly established risk factor in coronary artery disease and percutaneous interventions. Diabetics typically have aberrations in platelet function, coagulation, endothelial function, and intra-luminal thrombosis, which are thought to be correlated to ischemic events after PCI (Jacoby and Nesto, 1992). In the interest of this subgroup, a sub-study of the EPISTENT trial was formed to analyse the combined effect of GP IIb/IIIa inhibitors and stent implantation on diabetic patients (Marso et al 1999, Cho et al 2000). Among diabetic patients, the combination of stent implantation and abciximab therapy did prove to be beneficial compared to the other treatment strategies. At six months, the composite endpoint was reduced by 48.3% (p-value=0.006) (Marso et al 1999). Similar significant reductions were also observed in the secondary composite endpoints of death or myocardial infarction and death or large myocardial infarction, and revascularization rates. Cho et al (2000) paid particular attention to diabetic women in their recently published paper. Again, the most favourable outcomes were observed within the first year of follow up in diabetic women receiving stent implantation and abciximab therapy, particularly in the primary composite endpoint and myocardial infarctions alone. Interestingly, however, these outcomes did not differ significantly between diabetic men and women. The independence of sex was also supported in a separate paper by Cho et al (2000) in the analysis of pooled data from EPIC, EPILOG and EPISTENT.

### *ERASER Trial*

In general, the EPISTENT trial provided solid evidence that in addition to standard care during stent implantation, abciximab can significantly reduce the rate of adverse clinical outcomes. These results, however, are





germane to the time period from which they were collected and cannot necessarily be extrapolated to current practice. In addition, previous stenting trials have shown significant reductions in rates of death and myocardial infarction, but the combination of abciximab and stent implantation did not significantly improve target vessel revascularization rates. Restenosis due to neo-intimal hyperplasia after stent placement continues to be a concern. The investigators of the Evaluation of ReoPro And Stenting to Eliminate Restenosis (ERASER) trial hypothesized that abciximab may reduce neo-intimal hyperplasia after stent implantation, and hence, inhibit restenosis. Patients from 17 centres were enrolled in this randomized, double blind, placebo-controlled trial between 1996 and 1997 (ERASER Investigators 1999). Eligible participants had a target coronary artery stenosis of  $\geq 50\%$  in a vessel of diameter 2.75 to 3.5 mm and were suited to implantation of a Palmaz-Schatz stent (15 mm). Patients were then randomized to one of the three treatment groups:

- Abciximab 0.25 ug/kg bolus plus 2 consecutive 12-hour 0.125 ug/kg/min abciximab infusions (n=75)
- Abciximab 0.25 ug/kg/bolus plus 12-hour 0.125ug/kg/min abciximab infusion plus 12-hour placebo infusion (n=79)
- Placebo bolus plus 2 consecutive 12 hour placebo infusions (n=71)

All patients received aspirin, and heparin (ACT of 250-300 seconds) was administered until immediately after the procedure to allow removal of the sheath 4 to 6 hours later. Ticlopidine was left to the physician's discretion. Evaluation took place in-hospital and at 6 months for clinical status, electrocardiography, angioplasty, and intra-vascular ultrasound (IVUS) imaging.

The primary efficacy endpoint in this trial was defined as the percent in-stent volume obstruction of the target lesion, as measured by IVUS at 6



months. Secondarily, quantitative coronary angioplasty (QCA) measured late loss and loss index. In this study, there was no significant difference among the treatment groups for any of these measures. This suggests that at this dose and duration of abciximab therapy, neo-intimal hyperplasia was not reduced. In terms of clinical efficacy, the composite endpoint of death, myocardial infarction or revascularization did not differ significantly among the groups (25.4% placebo vs 21.4% combined abciximab,  $p>0.05$ ) (ERASER investigators 1999). Whether GP IIb/IIIa inhibition truly diminishes the growth of the neo-intima, and hence, reduces the occurrence of restenosis is still up for debate.

### *RAPPORT Trial*

The ReoPro in Acute myocardial infarction and Primary PTCA Organization and Randomized Trial (RAPPORT) is the largest trial to evaluate the outcomes in patients undergoing direct angioplasty (Brener et al 1998). In this randomized, placebo-controlled trial, 483 patients presenting with a ST-segment elevation acute myocardial infarction were assigned to either a placebo ( $n=242$ ) or to a 0.25 ug/kg abciximab bolus plus 0.125 ug/kg/min 12-hour infusion ( $n=241$ ) after undergoing emergency cardiac catheterization.

After 30 days of follow-up, the relative risk of the composite incidence of death, myocardial infarction and urgent revascularization was reduced by 48.2% ( $p\text{-value}=0.03$ ). When these patients were evaluated at six months, the effect was maintained (34.8%,  $p\text{-value}=0.048$ ). Interestingly, the incidence of urgent revascularization was significantly reduced in the abciximab-treated group compared to the placebo at 7-, 30- and 180-days. However, when all revascularization procedures were considered, statistical significance was lost. The loss of effect suggests that abciximab



therapy is most beneficial to direct angioplasty patients early in the treatment course, and revascularization for any reason is not influenced.

Bleeding complications were nearly doubled in the abciximab group (16.6% vs 9.5%). This is likely attributable to the late sheath removal and higher doses of heparin than are used in current practice. EPIC trial experienced similar problems.

### *CADILLAC Trial*

The Controlled Abciximab and Device Investigation to Lower Late Angioplasty (CADILLAC) trial is another trial on the horizon (Stone 1998). Its focus is to reveal the effectiveness of glycoprotein IIb/IIIa inhibition with coronary stent implantation as the primary treatment for acute myocardial infarction. Eligible patients will be allocated to one of four treatment arms:

- PTCA (n=516)
- PTCA plus abciximab (n=529)
- Primary stenting plus abciximab (n=512)
- Primary stenting with Multi-link<sup>®</sup> stent (n=525)

Endpoints of interest will include incidences of death, re-myocardial infarction, and urgent revascularization. Preliminary results presented at the 2001 American College of Cardiology Conference that cardiac death rates at 6 months were not significantly different between the four treatment groups (Grines et al 2001).

### *ADMIRAL Trial*

The ADMIRAL investigators had an objective similar to the CADILLAC investigators as they were seeking to understand the relationship between abciximab as an adjunct to stenting in acute myocardial patients. Across 30 centres in France, 300 patients with acute myocardial infarction were



randomly assigned to abciximab plus stent or placebo plus stent before coronary angiography (Barragan et al 2000). The investigators were interested in the composite endpoint of all-cause mortality, re-myocardial infarction or *urgent* target vessel revascularization within 30 days and 6 months of randomization. A secondary endpoint included the same components except for 'any revascularization procedure' instead of only urgent procedures. A preliminary analysis was presented at the latest American Heart Association Conference in November 2000. As indicated in Table 2.2, patients who received abciximab in conjunction with stenting fared significantly better than those who did not receive abciximab at 30 days and 6 months.

In general, the trials to date overwhelming support the use of abciximab as an adjunct therapy to percutaneous coronary interventions. Even as an adjunct to stenting compared to angioplasty, benefits have been realized. In a pooled analysis of EPILOG and EPISTENT trials the investigators noted that stenting plus abciximab did provide additional benefit over balloon angioplasty plus abciximab, which was revealed in lower rates of revascularization within one year (19.7% vs 24.4%, ( $p < 0.05$ ) respectively) (Cura et al 2000). However, abciximab as an adjunct to stenting did not significantly reduce the incidence of death or myocardial infarction within one year when compared to patients receiving balloon angioplasty plus abciximab (8.0% vs 7.6%, ( $p > 0.05$ ) respectively) (Cura et al 2000).

Rarely has a pharmacological agent had so great of an impact on clinical outcomes. However, its economic consequences may limit its use in clinical practice. For instance, the cost of abciximab in 1998 was US\$1407 per patient, which obviously presents a challenge to institutions that are concerned about cost-containment (Hillegass et al 1999). However, less





expensive alternatives, eptifibatide and tirofiban, are under investigation in the hopes that cost-effectiveness will be maximized.

## 2.4 EPTIFIBATIDE

In 1998, eptifibatide was approved for use in the United States. Two trials, IMPACT-II and the PURSUIT trials, provided the body of evidence to supports its use as an adjunct to percutaneous coronary interventions and for the management of unstable angina and non-ST-segment elevation myocardial infarction, respectively. However, these trials were conducted in the mid-nineties before the widespread use of coronary stenting. An emerging trial, the Enhanced Suppression of the Platelet GP IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial will assess the safety, efficacy, and cost-effectiveness of eptifibatide in the current environment of stent implantation (2000).

Table 2.3. Clinical trials of eptifibatide and PCI.

Authors	Patients	Interventions	Outcomes	Results
IMPACT-II Investigators	N=4010 (elective, urgent or emergent) PCI patients, all treated with ASA, between November 1993 and November 1994.	1.Placebo (n=1328) (Ref) 2.Ept (low dose) (n=1349) 3.Ept (high dose) (n=1333)	Composite endpoint: 1) All-cause mortality 2) MI 3) Repeat PCI 4) CABG 5) Stent, At 30 days.	Composite endpoint: <u>30 days</u> : low dose 11.4%vs9.2% RRR=19.3% p=0.063. high dose 11.4%vs9.9% RRR=13% p=0.22.
Kleiman et al for the PURSUIT Investigators	Subset of the full trial N=1228 with ACS, underwent early PCI within 72 hours of randomization, all treated with ASA (& heparin was recommended), between Nov. 1995 and Jan. 1997.	1.Placebo (n=622) (Ref) 2.Ept (n=606)	Composite endpoint: 1) All-cause mortality 2) MI At 30 days.	Composite endpoint: <u>30 days</u> : 16.7% vs 11.6% RRR= 31% p=0.010.



Authors	Patients	Interventions	Outcomes	Results
ESPRIT Investigators	N=2064 underwent elective PCI with stent, all treated with ASA, thienopyridine & heparin between June 1999 and February 2000.	1. Placebo (n=1039) 2. Ept (n=1023)	Composite endpoint: 1) All-cause mortality 2) MI 3) Urgent revasc. 4) Thrombotic bailout therapy  At 2 days. Secondary composite: 30days 1) All-cause mortality 2) MI 3) Urgent revasc.	Composite endpoint: <u>2 days:</u> 10.6% vs 6.6% RRR=38% p<0.005          <u>30 days:</u> 10.6%vs6.8% RRR=35% p<0.005

OR, odds ratio; HR, hazard ratio; Ref, reference group; RRR, relative risk reduction; vs=versus.

### *IMPACT-II Trial*

The Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-II (IMPACT-II) was one of the first large-scale trials to examine the efficacy of eptifibatide. This double-blind, placebo-controlled clinical trial enrolled 4010 patients undergoing elective, emergent or emergency percutaneous coronary interventions in 82 sites in the United States of America between 1993 and 1994 (IMPACT-II Investigators, 1997). The specific goals of the trial were threefold: (1) to assess the efficacy of eptifibatide in patients of all risk categories, (2) to compare different infusion rates (0.50 ug/kg/min versus 0.75 ug/kg/min) when given identical bolus (135 ug/kg), and (3) to consider the safety of eptifibatide with concomitant heparin and aspirin. The purpose of the low-dose treatment was to allow gradual recovery of platelet function over the course of infusion and to minimize bleeding complications and thrombocytopenia, which are associated with GP IIb/IIIa inhibition. The purpose of the high-dose was to maintain platelet inhibition. Patients were prospectively risk stratified, and were considered high risk if they were enrolled within 24 hours of the onset of symptoms of acute



myocardial infarction and were to undergo direct or rescue PCI, or if they had unstable angina or non-Q-wave myocardial infarction; all other patients were classified as low-risk (58.9% of the study population). Balloon angioplasty, directional coronary atherectomy, rotational atherectomy, or excimer laser ablation were initiated within 10-60 minutes of onset of study treatment. Stent implantation was allowed only if there was a threatened or actual abrupt vessel closure.

The primary composite endpoint included death, myocardial infarction, urgent revascularization or emergent stent placement within 30 days. In the intention-to-treat analysis, 11.4% of placebo group experienced the endpoint, compared to 9.2% in the 135/0.5 group (low-dose) and 9.9% in the 135/0.75 group (high-dose). A decreasing trend in the incidence of the endpoint was noted even though statistical significance was not reached in either comparison (p-values=0.063 and 0.22, respectively). However, in the analysis of outcomes in patients who actually received the study drugs, there was a significant difference between the placebo (11.6%) and the low dose group (9.1%, p-value=0.035). Across all components of the primary composite endpoint, the low-dose group continually experienced better outcomes.

The inappropriate type of anticoagulant and subsequent under-dosing may explain these unexpectedly diluted results. According to Phillips et al (1997), if levels of free ionized calcium in the blood are low then the degree of platelet inhibition by eptifibatide is high, and vice versa. To inhibit coagulation, citrate was added to the blood sample of patients who received eptifibatide. And when done so, citrate competitively binds to the ionized calcium, thereby decreasing the pool of free ionized calcium, which then over-estimated the degree of platelet inhibition. In fact, only 60% platelet inhibition was achieved in the IMPACT-II trial, which is significantly



lower than the standard target of >80%. To attain this desired target, later trials used D-phenyl-alanyl-prolyl-arginine chloromethyl ketone (PPACK) as the anticoagulant to establish the appropriate dose of 180ug/kg bolus plus 2.0ug/kg/min infusion (PURSUIT Investigators 1998).

In addition to the under-dosing, several unexpected results were generated. Firstly, the administration of eptifibatide was not associated with significant increase in the incidence of major bleeding, transfusions or thrombocytopenia, and in fact, these complications were similar across all three treatment groups. Secondly, risk stratification did not appear to be predictive of the outcomes. The investigators reported that in the placebo-group, the incidence of the primary composite endpoint at 30 days was slightly higher in the low-risk than in the high-risk stratum. Recently, Thel et al (2000) published additional results from the IMPACT-II trial to further probe the utility of risk stratification. Specifically, they looked at the time course and risk factors for adverse clinical events after percutaneous coronary intervention. Patients are at greatest risk within the first 6 to 9 hours after the intervention. Predictors of early events (<6 hours) included dissection, pre- and post-procedural coronary blood flow, side-branch occlusion, procedural thrombolytic use, previous bypass, presentation with unstable angina, absence of diabetes, and hyperlipidemia. Independent predictors of late events ( $\geq 6$  hours) included lower weight, increased baseline heart rate, coronary dissection, and procedural thrombolytic use. It is hoped that this information will aid in the risk stratification of patients before and after intervention for ischemic events.

### *PURSUIT Trial*

As mentioned above, the IMPACT-II trial was riddled with unusual results, which were later resolved with more accurate dosing. The impetus of the Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression





Using Integrilin Therapy (PURSUIT) trial was to confirm the appropriate dose of eptifibatide in a broad range of acute coronary syndromes, excluding ST-segment elevation myocardial infarctions. This trial enrolled and randomly assigned 10 948 patients from North American, Western Europe, Eastern Europe and Latin America to one of three treatment arms:

- Low-dose eptifibatide (180 ug/kg bolus plus 1.3ug/kg/min infusion) (n=1487)
- High-dose eptifibatide (180 ug/kg bolus plus 2.0 ug/kg/min infusion) (n=4722)
- Placebo (n=4739)

Infusions lasted up to 72-96 hours. All patients received concomitant aspirin and heparin therapies. The lower-dose arm was discontinued after an early analysis of the data confirmed the safety of the higher-dose, and subsequent analyses compare the high-dose group to the placebo. The primary composite endpoint was defined as the incidence of death from any cause or non-fatal myocardial infarction at 30 days. Secondary endpoints included all-cause mortality within 30 days, first or recurrent myocardial infarction, the primary composite endpoint at 96 hours and 7 days, measures of safety and efficacy of treatment in patients undergoing percutaneous revascularization (e.g., PTCA) (PURSUIT Investigators 1998).

In the overall study population, the primary composite endpoint was reduced from 15.7% with placebo to 14.2% (p-value=0.04) with eptifibatide. Interestingly, the greatest risk reduction was found in the 1228 patients who underwent early PCI (i.e., within 72 hours of randomization) (16.7 % with placebo vs 11.6% with eptifibatide, relative reduction=30.5%, p-value=0.01); for those who did not undergo early PCI, there was a 7.0% risk reduction (p-value=0.23). When the composite endpoint was broken



down by time points covering before and after PCI, patients receiving eptifibatide experienced a reduction of 69.0 % in the primary composite endpoint of death or non-fatal myocardial infarction before early PCI (p-value<0.001). Measures at subsequent time points did reveal a beneficial trend in favour of eptifibatide but they did not yield statistically significant reductions. Notably, the treatment effect was not affected by the time-to-PCI (Lorenz et al 1999).

With respect to safety endpoints, bleeding, red blood cell transfusions, and thrombocytopenia were more common in patients receiving eptifibatide than placebo. However, there was no increase in intra-cranial haemorrhage between the groups and the majority of the bleeding complications were minor (according to the TIMI scale (Rao et al 1988)). The frequency of major bleeding could be attributed to the patients who received CABG surgery. Even with the CABG cases removed, major bleeding was significantly higher in the eptifibatide group (3.0% versus 1.3% with placebo; p-value<0.001), and most often occurring at the femoral artery access site in those undergoing percutaneous coronary intervention. Transfusions occurred more often in eptifibatide-treated patients than in the placebo (11.6% vs 9.2%; p-value<0.05). Severe thrombocytopenia (<50 000 platelets/mm<sup>3</sup>) was rare but eptifibatide-treated patients did suffer more often than placebo-treated (0.2% vs <0.1%; p-value<0.05). In a recently published report from the PURSUIT trial, the investigators tried to establish causality between thrombocytopenia and adverse complications in patients receiving eptifibatide (McClure et al 2000). Although this could not be done, a clear correlation between thrombocytopenia and adverse clinical outcomes (both safety- and efficacy-related) was confirmed.



### *ESPRIT Trial*

As described earlier, the ESPRIT Investigators hoped to shed light on the current scene of interventional cardiology. This was the only trial to specifically address the use of stents with eptifibatide as adjunctive therapy. The ESPRIT trial was designed as a multi-centred, randomized, parallel-group, placebo-controlled clinical trial in North America. This trial had three focal points: (1) the under-dosing of eptifibatide in IMPACT-II, (2) the brisk evolution of PCI practices since IMPACT-II (e.g., lower procedural heparin dosing and increased use of ticlopidine or clopidogrel), and (3) the increasing use of GP IIb/IIIa inhibitors as bailout therapy in PCI (O'Shea et al 2000).

Upon enrolment, all patients received aspirin, weight-adjusted heparin, and ticlopidine or clopidogrel. Random allocation to the eptifibatide group or the placebo occurred upon administration of the study drug. The target platelet inhibition of >80% was achieved through two 180ug/kg boluses 10 minutes apart and an infusion of 2.0 ug/kg/min for 18-24 hours. Unlike previous studies, a heparin regimen was recommended with a target activated clotting time of 200-300 seconds.

The primary efficacy endpoint is a composite of death, myocardial infarction, urgent target revascularization, and thrombotic bailout GP IIb/IIIa therapy within 48 hours of randomization, and was assessed at 30 days. Safety endpoints included the incidence of major bleeding according to the TIMI criteria and thrombocytopenia, and was evaluated at 48 hours or at time of discharge, whichever came first.

Upon recommendation from the Data and Safety Monitoring Board, enrolment in the ESPRIT trial was terminated at 2064 participants due to significance of the effect in the preliminary analysis. According to the



analysis of the 48-hour data of 1758 patients, death or MI had occurred in 8.6% of the placebo-treated patients and in 4.9% of the eptifibatide group (43.0% risk reduction, p-value<0.01). Based on this significant reduction in the endpoint at 48 hours, enrolment into the trial ended.

The results of the full study population at 48 hours and 30 days were presented at American College of Cardiology Conference in February 2001 (Tcheng et al 2001). Based on the final study population of 2064 patients, the primary endpoint at 48 hours was reduced from 10.6% to 6.6% (p<0.005) with the administration of eptifibatide. At 30 days, similar benefits were realized (10.5% (placebo group) vs 6.8% (eptifibatide group) (p<0.005)).

2.5 TIROFIBAN

A handful of trials have been designed to assess the safety and effectiveness of tirofiban in the patients undergoing percutaneous coronary interventions. In this review, RESTORE, PRISM-PLUS and TACTICS-TIMI-18 will be discussed.

Table 2.4. Clinical trials of tirofiban and PCI.

Authors	Patients	Interventions	Outcomes	Results
RESTORE Investigators	N=2141 with ACS, treated with ASA and heparin & underwent PTCA or DCA between January 1995 and December 1995.	1. Placebo (n=1070) (Ref) 2. Tirofiban (n=1071)	Composite endpoint: 1) All-cause mortality 2) MI 3) CABG 4) Repeat PCI 5) Stent placement, At 2, 7, 30, 180 days.	Composite endpoint: <u>2 days:</u> 8.7% vs 5.2% RRR=40%p<0.01 <u>7 days:</u> 9.8% vs 6.9% RRR=30%p<0.05 <u>30 days:</u> 10.5% vs 8.0% RRR=24%p<0.20 <u>180 days:</u> 27.1% vs 24.1% RRR=11%p>0.10





Authors	Patients	Interventions	Outcomes	Results
PRISM-PLUS Investigators	N=475 patients underwent angioplasty. (A substudy of the original 1570 patients with UA/ non-Q-wave MI between November 1994 and September 1996.)	1.Heparin (n=236) (Ref) 2.Tirofiban & heparin (n=239)	Composite endpoint: 1) All-cause mortality 2) MI 3) Refractory ischemia after 7 days At 30, 180 days.	Composite endpoints: <u>30 days:</u> 15.2% vs 8.8% RRR=42% OR=0.528 95%CI (0.297, 0.940) <u>180 days:</u> 30.9% vs 24.7% RRR=20% OR=0.734 95%CI (0.521, 1.035)

OR, odds ratio; HR, hazard ratio; Ref, reference group; RRR, relative risk reduction; vs, versus; UA, unstable angina.

### *RESTORE Trial*

The RESTORE trial was the first clinical trial designed specifically to evaluate the safety and effectiveness of tirofiban in patients undergoing percutaneous coronary interventions (e.g., PTCA (balloon angioplasty) or direct coronary atherectomy (DCA)) within 72 hours of presentation of unstable angina or acute myocardial infarction. Patients were excluded on the basis of prior thrombolytic therapy (within 24 hours), contraindication to anticoagulation, prior platelet disorder or thrombocytopenia, history of stroke or other intra-cranial pathology, or were scheduled for elective stent placement or if angioplasty with rotablator or transluminal extraction catheter device was planned (RESTORE Investigators 1997). All patients received aspirin and weight-adjusted heparin before randomization. The treatment arms began at the time of the procedure and continued for 36 hours and are as follows:

- Tirofiban (10ug/kg bolus over 3 minutes plus infusion of 0.15 ug/kg/min) (n=1071)
- Placebo (n=1070)



The endpoints were all-cause death, myocardial infarction, CABG due to angioplasty failure or recurrent ischemia, repeat angioplasty for recurrent ischemia, insertion of a stent due to threatened or actual abrupt vessel closure, and a composite endpoint that embodied the occurrence of any of the aforementioned events.

The most striking results were observed soon after the coronary intervention. At 2 and 7 days there were statistically significant reductions in both the composite and the myocardial infarction endpoints (37.9% relative risk reduction  $p < 0.01$ , 26.9% relative risk reduction  $p < 0.05$ , respectively, RESTORE 1997 and 1998). However, at 30 days and 6 months, the difference in the composite endpoint was not statistically significant (30 days: 23.8% relative risk reduction  $p > 0.05$ ; 6 months: 11.1% risk reduction  $p < 0.11$ ) (Gibson et al 1998). It seemed that the benefits of tirofiban on the composite endpoint was degrading with time. This is not surprising since tirofiban's actions are short-lived, unlike abciximab.

RESTORE differs from the EPIC and EPILOG trials in that the definition of the revascularization component of the composite endpoint. In abciximab trials, only urgent revascularizations were included, whereas RESTORE includes all revascularization. Upon re-adjudication of the endpoint to include only emergent revascularization, the clinical outcomes did not change substantially (RESTORE 1997).

In terms of bleeding complications, the major bleeding events (TIMI definition: decrease in hemoglobin level  $> 5\text{g/dL}$  or intracranial bleed) and thrombocytopenia (defined as platelet count  $\leq 90\,000$  per  $\text{mm}^3$ ) were infrequent and often did not reach statistical significance. In the PRISM-PLUS trial (discussed below), a relative risk increase of 33% was noted in tirofiban-plus-heparin treatment arm ( $p\text{-value}=0.23$ ). However, in the



RESTORE trial, a lower relative risk increase (14.3%; p-value=0.662) was observed. Thrombocytopenia is another concern in this drug class. In the PRISM-PLUS trial, thrombocytopenia was uncommon but was close to statistical significance in 1.9% of the tirofiban-plus-heparin group (p-value=0.07 compared to the placebo group). In the RESTORE trial, this phenomenon occurred in 1.17% patients receiving tirofiban (p-value=0.831).

### *PRISM-PLUS Trial*

The Platelet Receptor Inhibition for Ischemic Syndrome Management-in Patients Limited to very Unstable Signs and Symptoms (PRISM-PLUS) trial differs from the RESTORE trial in that patients with unstable angina or non-Q-wave myocardial infarction were not exclusively treated with PCI. This trial enrolled 1915 patients in 72 hospitals from 14 countries between November 1994 and September 1996 (PRISM-PLUS Investigators, 1998). The trial design involved the double blind random allocation of patients to receive one of three regimens:

- Tirofiban (0.6 ug/kg body weight per minute for 30 minutes plus an infusion of 0.15 ug/kg/min) plus heparin placebo. (n=345)
- Tirofiban (0.4 ug/kg/min for 30 mins plus an infusion of 0.1 ug/kg/min) plus adjusted-dose heparin. (n=797)
- Adjusted-dose heparin plus tirofiban placebo. (n=773)

The study drugs were infused for a minimum of 48 hours after randomization and coronary interventions were delayed until after this time unless it was called for by refractory ischemia or by a new myocardial infarction. Angiography and angioplasty (if indicated) were performed between 48 and 96 hours after randomisation while continuing to administer the study treatments. The tirofiban-only arm was discontinued



early on in the trial period due 16 deaths out of 345 patients in this treatment arm at seven days.

Within the study population, 30.5% underwent a percutaneous coronary intervention during the initial hospitalization. This subgroup allowed for the evaluation of tirofiban therapy before and after PCI on clinical outcomes. One caveat of the subgroup analysis is that percutaneous procedures were not randomly assigned, and were likely influenced by the patient's clinical course and coronary anatomy (PRISM-PLUS 1998). But because the number of patients undergoing angioplasty was equal in both treatment groups, it seems the decision to undergo angioplasty was likely affected by coronary anatomy (Cook et al 1999). With these limitations in mind, outcomes at 30 days after angioplasty were visibly improved in patients receiving both tirofiban and heparin. All-cause death, myocardial infarction, refractory ischemia, or re-hospitalization for unstable angina occurred during or after angioplasty in 21 of 239 patients (8.8%) in tirofiban treatment arm, and in 36 of the 236 in the heparin-only arm (15.2%) (risk ratio of 0.55; 95% confidence interval (0.30-0.94)). The composite endpoint of death or myocardial infarction was 5.9% and 10.2%, respectively (risk ratio 0.56, 95% confidence interval (0.29-1.09)). Similarly, the suppression of these endpoints in the tirofiban and heparin arm was observed at 6 months (Cook et al 1999).

Diabetic patients are often at a significant disadvantage compared to non-diabetic patients in terms of prognosis of acute coronary syndromes. Recently, the results from a retrospective subgroup analysis on diabetic patients were published (Theroux et al 2000). Of the patients on the heparin treatment arm, 21.9% were diabetic, and of the tirofiban and heparin arm, 24.2% were diabetic. When compared to non-diabetic patients, diabetic patients had a higher incidence of prior coronary artery





disease and prior coronary artery procedures, hypertension, hypercholesterolemia, and ST-segment depression (Theroux et al 2000). This trend was also observed in the primary composite endpoint of the study but with no statistical significance at any time point. Within the diabetic patients, those who received tirofiban and heparin did have a lower cumulative incidence of the composite endpoint but it was not statistically significant at 6 months (p-value=0.11). However, there was a significant reduction in the death and myocardial infarction composite endpoint at 6 months for those who were on the combination therapy (p-value=0.03).

### *TACTICS-TIMI 18 Trial*

The TACTICS-TIMI 18 trial is an emerging endeavour that will attempt to evaluate the effects of tirofiban in the context of current treatment options available to acute coronary syndrome patients. The rationale behind the TACTICS-TIMI 18 trial is to reveal whether invasive or conservative treatment results in the best clinical outcomes in the present environment of GP IIb/IIIa inhibitors (e.g., tirofiban), cardiac enzyme markers and coronary interventions (Cannon et al 1998). Initially all patients presenting with unstable angina or non-Q-wave myocardial infarction will be given aspirin, heparin, and tirofiban. After that, patients will be randomized in a 1:1 ratio to either the early invasive treatment course or to the conservative medical management approach. The investigators hypothesize that the early invasive therapy will produce better clinical outcomes in terms of lower incidences of death, acute myocardial infarction and re-hospitalization for ACS at six months than those on the conservative route.

In addition to clinical outcomes, quality of life will also be assessed (Weintraub et al 1999). Quality of life has rarely been measured or reported in any of the acute coronary syndromes clinical trials. However, a growing



number of people are interested in the patient's perspective of these therapies. Like the APPROACH database, which is the data source in this thesis, the TACTICS-TIMI 18 trial will use the Seattle Angina Questionnaire (SAQ). SAQ covers 5 clinically important areas: physical limitations, stability of angina, frequency of angina, treatment satisfaction, and disease protection (Spertus et al 1994). This questionnaire has been carefully translated into 12 other languages; thus, international comparisons and the aggregation of data are not in jeopardy. In addition, the TACTICS-TIMI 18 group will be using the Health Utilities Index (HUI), which will provide a description of the influence of treatment strategies on general health status (Weintraub et al 1999). By using both of these instruments, the current knowledge gap of patients' quality of life should be narrowed.

## 2.6 SUMMARY AND FUTURE DIRECTIONS

Overall, the clinical trials of the 1990s provided substantive evidence of the efficacy of GP IIb/IIIa inhibition, especially as an adjunct to PCI. However, much work remains. None of these trials compared these three agents directly and as such, inferences cannot be made about the relative effectiveness of these three agents. In attempts to replace that missing link, the Do Tirofiban and ReoPro Give Similar Efficacy Outcomes Trial (TARGET) was designed to directly compare tirofiban and abciximab during percutaneous coronary intervention and stent placement (Moliterno et al 2000). It is also the largest prospective trial to involve stent placement (anticipated n=4300). The aim of the trial is to assess the efficacy of tirofiban in patients undergoing non-emergency PCI with an intracoronary stent and to compare the efficacy of tirofiban to abciximab at 30 days, 6 months and 1 year. In addition, the protocol was designed to reflect the current 'real world' approach to treatment. For example, any approved revascularization device is allowed, and second and third generation stents will be used. In addition to being the first direct comparison between



tirofiban and abciximab, the TARGET trial should also supplement the findings of the EPISTENT and ESPRIT trials by providing a snapshot of the current PCI scene.

Recently, a second direct comparison trial was announced. The Prairie ReoPro versus Integrilin Cost Evaluation (PRICE) trial will examine the pharmacodynamics, clinical outcomes and economic impact among patients randomly assigned to abciximab (ReoPro) or eptifibatide (Integrilin) (The PRICE Investigators 2001). This randomized, double blind study has enrolled 320 consecutive patients who underwent elective balloon angioplasty or stent implantation. These patients were randomly assigned to receive abciximab (n=163) or eptifibatide (n=157) as adjunct therapy to PCI. The composite endpoint (all-cause death, myocardial infarction and urgent revascularization) did not differ significantly between the two agents (in-hospital: 4.9% (abciximab) vs 5.1% (eptifibatide)  $p=0.84$ ; 30 days: 5.6% (abciximab) vs 6.3% (eptifibatide)  $p=0.95$ ). However, significant reductions in both in-hospital and 30-day costs incurred by patients who received eptifibatide were revealed. It will be interesting to see if these results carry over when larger cohorts of patients are studied.

The upcoming years will also provide an opportunity for the refinement of the use of GP IIb/IIIa inhibition in acute coronary syndromes in contemporary practice. For example, the GUSTO-IV ACS trial will evaluate the efficacy of conservative medical management (e.g., abciximab therapy) in patients with non-ST-segment elevation acute coronary syndromes, (Lincoff 2000). Essentially, the driver behind this trial was to assess the effect of abciximab on a more homogeneous population of non-ST-segment ACS, and thus, refining the true effect on this group of patients. Some investigators felt that the effect of GP IIb/IIIa inhibition in unstable angina patients was diluted by the heterogeneity of patients (Lincoff 2000).



The advances in diagnostic tools since the earlier trials of this genre should help to clear up these differences. GUSTO-IV AMI will build upon the successful results of the TIMI-14 and SPEED trials by investigating the efficacy of abciximab in conjunction with reduced-dose fibrinolytics (e.g., reteplase). With the results of these trials still pending, the GUSTO-IV ACS and GUSTO-IV AMI trials may provide evidence that the administration of abciximab will improve clinical outcomes and broaden therapeutic options in patients suffering from a wide variety of acute ischemic conditions (Lincoff 2000).





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## CHAPTER 3: OBJECTIVES AND HYPOTHESES

As highlighted in the two preceding chapters, the volume of evidence for GP IIb/IIIa platelet receptor inhibitors supports its use as an adjunct therapy to PCI. However, its use and effect in routine medical care is not well documented. In these times of limited healthcare resources, the knowledge of the utilization, effectiveness and cost-effectiveness of this or any technology is becoming increasingly important. In response to these concerns, the current study will examine two of the aforementioned components: the utilization and effectiveness of abciximab as an adjunct to PCI in the Province of Alberta. More specifically, the following questions will be addressed:

1. Did Alberta residents who underwent PCI between January 7, 1999 and December 31, 1999 and were considered high-risk patients receive abciximab more often than moderate- and low-risk patients?

### Hypothesis and Rationale for Hypothesis:

Evidence from the clinical trials indicates that the benefits of abciximab span across all risk strata. Despite these gains, this therapy costs average cost of \$1694 per treatment (1998/99), which poses a significant burden on already limited health care resources (R. Muzyka, Personal Communication). In response, the provincial health authorities placed a funding ceiling on this therapy to 25% of all PCIs and recommended its use among high-risk patients (R. Muzyka, Personal Communication). Thus, it was hypothesized that in this population of PCI patients, those at high-risk would receive abciximab more often than the patients in lower risk strata.



2. Were Alberta residents who underwent PCI between January 7, 1999 and December 31, 1999 and received abciximab therapy at a lower risk of death or repeat revascularization within one year of the procedure than those who do not receive abciximab?

#### Hypothesis and Rationale for Hypothesis:

In the majority of clinical trials, clinical endpoints such as rates of death and repeat revascularization within various time periods were reduced by the use of abciximab. In the patient population of the current study, it was expected that the rates of death and repeat revascularization within one year would be lower in the patients who received abciximab therapy than those who did not.

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## CHAPTER 4: DESCRIPTION OF THE DATA SOURCE

Since January 1995, the Alberta Provincial Program for Outcome Assessment in Coronary Heart Disease (APPROACH) project has served as a window into the cardiac services provided in Alberta. This ongoing population-based data collection initiative captures information on all patients undergoing cardiac catheterization procedures in Alberta (Ghali and Knudtson 2000). In particular, an impressive array of data is collected on sociodemographic measures (age, sex, postal code), comorbidities, prior and recent cardiac-specific events, coronary anatomy, subsequent treatment strategies, and data on short- and long-term clinical outcomes (i.e., death and repeat revascularization procedures) (Davies 2000). In addition to these data, the APPROACH database is linked to data on mortality from the Alberta Bureau of Vital Statistics, hospital separation data and data from follow-up surveys of quality of life outcomes at 1, 3 and 5 years post catheterization (Ghali and Knudtson 2000).

Currently, cardiac catheterizations are taking place at three catheterization laboratories in Alberta: Foothills Hospital (Calgary), Royal Alexandra Hospital (Edmonton) and University of Alberta Hospitals (Edmonton). Approximately 7000 new patients undergo cardiac catheterization each year in Alberta, and overall enrolment for the APPROACH project included over 35 000 patients as of December 1999. Inception of data collection at the point of cardiac catheterization provides an opportunity to observe patients through several different treatment courses (i.e., PCI, CABG or medical therapy). However, a significant number of patients with coronary artery disease (CAD) may be excluded. Some patients suffering from CAD may fail to present for medical care or may receive care but never enter a cardiac catheterization laboratory (Ghali and Knudtson 2000).





An attractive feature of the APPROACH project is its ability to study treatment courses and outcomes of cardiac procedures at the population level (Davies 2000). This population-based design has effectively reduced the bias that may arise due to selection of a convenient sample from a single referral center or those receiving a single treatment (e.g., CABG or PCI) (Ghali and Knudtson 2000). This allows the data set to be used at the local hospital level as well as in national level comparisons.

The potential impact of the APPROACH project is great. The efforts of the last six years have established the APPROACH project as a reliable and valuable tool in cardiac outcomes research in Alberta and Canada.

Because of the comprehensiveness of the data and its ease of implementation and operation in the cardiac catheterization laboratory, several sites in other provinces, such as British Columbia, Ontario and Saskatchewan have joined this data collection initiative. In the coming months, Manitoba and Nova Scotia will be among the most recent sites to be added to the list.

Also, this rich data source provides opportunities to support a wide variety of clinical and research needs. Specifically, the APPROACH project can sustain the determination of short- and long-term clinical, economic and quality of life outcomes, the evaluation practice patterns with respect to new technologies (i.e., devices, drugs, etc.), and the tracking of resource use and their associated costs. Eventually, the evidence generated from APPROACH may be used to advise clinicians, patients, researchers, administrators, health policy-makers and pharmaceutical and device industries.

Definitions of terms and the PTCA data entry form from the APPROACH project protocol are presented in Appendix I.



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## CHAPTER 5: METHODS

### 5.1 STUDY POPULATION SELECTION

As described in the previous chapter, the APPROACH database contains data on all cardiac catheterization procedures performed at the Foothills Hospital (Calgary), Royal Alexandra Hospital (Edmonton), and University of Alberta Hospital (Edmonton). If consent is received from the patient, data is collected on subsequent treatment modalities (CABG and/or PCI), quality of life and survival.

Between January 7, 1999 and December 31, 1999, 3251 PCI procedures were carried out at the three above-mentioned sites. Although abciximab was first introduced to Alberta clinical practice in July 1997, it was assumed that data on this therapy would be appropriately collected within the two years of abciximab's introduction.

Based on the objectives of the study, several steps were taken to further define the study population (Figure 5.1). First, only residents of the Province of Alberta were selected because of the increased assurance that these patients could be followed up. Unique personal health numbers and postal codes identified residents of Alberta. Thus, from the original 3251 PCI procedures, data on 259 non-Alberta resident procedures were eliminated. Another 44 records were eliminated due to missing values on key variables such as coronary anatomy. Finally, if a patient had undergone more than one PCI procedure during the study period, data on the subsequent procedures were not used. This final step moved the analyses from procedure-based to patient-based.

In the final analyses, data for the residents of the Province of Alberta who had undergone their first PCI (hereafter referred to as the 'index PCI')

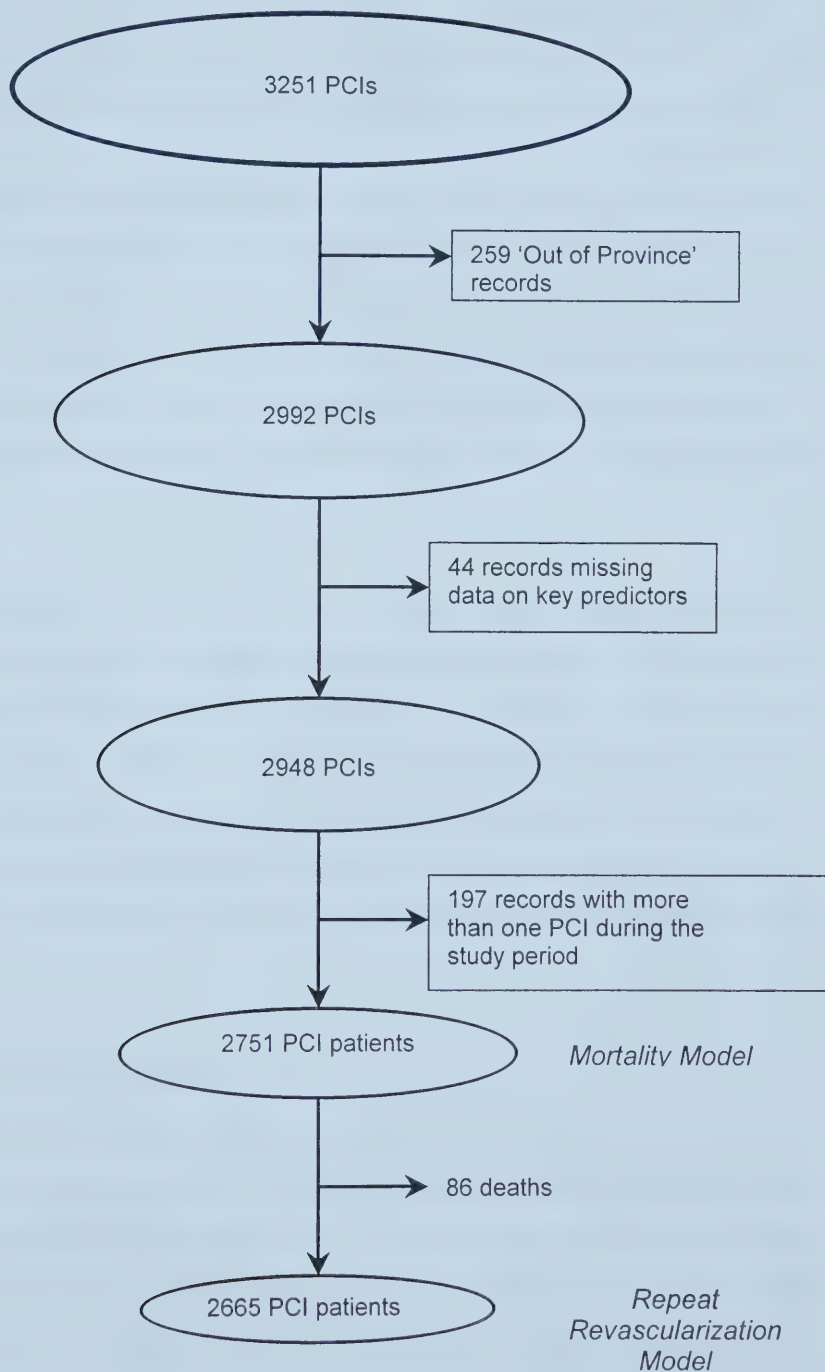


during the calendar year of 1999 were included (n=2751 (mortality model), n=2665 (repeat revascularization model)). Within each of these models, the patients who received abciximab were compared to those who did not.





Figure 5.1. Flowchart of study population selection.





## 5.2 DEFINITIONS OF OUTCOMES

The current study examined two outcomes: (1) all-cause mortality rate within one year of the index PCI; and (2) repeat revascularization procedure rate (repeat PCI or CABG) within one year of the index PCI.

The majority of clinical trials and population-based studies in this area have also included the occurrence or recurrence of myocardial infarction as an endpoint or as part of a composite endpoint (EPIC 1994, CAPTURE 1997, EPILOG 1997, Brener et al 1998, EPISTENT 1998, O'Donnell et al 1999, Zwart-van Rijkom et al 2001). Unfortunately, the APPROACH database does not collect data on this outcome and thus, it was not examined in this study.

Of the few published *population-based* studies of the effects of PCI and abciximab, most have reported on short-term outcomes (i.e., in-hospital, 30 days and/or 6 months) (Velianou et al 2000, Plucinski et al 2000, Zwart-van Rijkom et al, 2001). Effects of abciximab in the long-term, however, have not been described as often in clinical practice. Consequently, this study chose to focus on the long-term outcomes (i.e., within one-year of the index PCI) in patients who received abciximab compared to those who did not.

### 5.2.1 *Death within one year of PCI*

In the APPROACH registry, patients' survival is verified via a bi-annual linkage with mortality data from the Alberta Bureau of Vital Statistics (Ghali and Knudston 2000). Due to the nature of the outcome, confidence in its documentation is high. Under ideal research conditions, the cause of death should be known in order to appropriately attribute a death to a specific cause. However, this information is not always available or complete. Of



the 94 deaths in the dataset of the current study (n=2751), the cause of death was listed for only 48 patients. And of those 48, 37 deaths were caused by cardiac-related disease or condition as indicated by the ninth revision of the International Classification of Disease (ICD-9) codes (i.e., ischemic heart disease (410-414), atrial fibrillation (427.3) and unspecified cardiovascular disease (429.3)). Other causes included several types of malignant neoplasms, diabetes mellitus, intra-cranial haemorrhage, arteritis, diverticulosis of the small intestine and fractures of the upper limbs, rib(s) and sternum.

Moreover, several researchers have voiced concern of the validity of the cause of death recorded on death certificates (Coady et al, 2001, Stehbens 1991 and 1993). On the basis of these reasons, this study examined all-cause mortality within one year of the index PCI as an outcome rather than cause-specific mortality.

### *5.2.2 Repeat revascularization within one year of PCI*

The second outcome of interest is the rate of repeat revascularizations within one year of the index PCI. In this study, a repeat revascularization procedure was defined as either a CABG or repeat PCI. Data on repeat revascularizations are routinely collected in the APPROACH database as part of its mandate to track all cardiac catheterization patients in the Province of Alberta. However, there is the potential for under-representation as the database may lose contact with patients who move out of the province, or, for whatever reason, may undergo these procedures outside of Alberta.



5.3 DEFINITIONS OF INDEPENDENT PREDICTOR VARIABLES

Several independent predictors were considered in the initial stages of the model building process for outcomes (Table 5.1). Detailed definitions of these terms can be found in the previous chapter.

Table 5.1. Independent variables considered when predicting the rate of outcomes within one year of the index PCI.

<i>Demographics</i>	<i>Comorbidities</i>		<i>History of Heart Disease</i>
Age	COPD	Renal dysfunction	Prior CHF
Sex	Diabetes	Liver/GI disease	Prior MI
	Malignancy	PVD	Prior PCI
	Hypertension	Hyperlipidemia	Prior CABG
	Past Smoker	Present Smoker	Prior thrombolytic therapy
	Cerebrovascular disease		
<i>Coronary Anatomy</i>		<i>Procedural Factors</i>	
# lesions >70% stenosis		MI on admission	CCS Angina Class
Graft		Cardiogenic shock	LVEF
Proximal LAD		Priority	Direct procedure
Left main artery disease		IABP	Stent
		Abciximab	Site of PCI(Hospital)
		Complete revascularization	

CABG=coronary artery bypass graft surgery; CCS=Canadian Cardiovascular Society; CHF=congestive heart failure; COPD=chronic obstructive pulmonary disease; GI=gastro-intestinal; IABP=intra-aortic balloon pump; LAD=left ascending coronary artery; LVEF=left ventricular ejection fraction; MI=myocardial infarction; PTCA=percutaneous transluminal coronary angioplasty; PVD=peripheral vascular disease; revasc=revascularization.

5.3.1 Coding of variables

The ‘age’ variable was a continuous variable and was coded in years. The number of lesions with >70% stenosis was the only other continuous variable. Sex was coded ‘0’ for males, and ‘1’ for females.

Variables of comorbidities, history of heart disease, presence/absence of proximal left anterior descending artery disease or left main artery disease and procedural factors were all dichotomous and coded ‘0’ for the absence of the condition and ‘1’ for its presence.





### *5.3.2 Creation of new variables*

Two new comorbidity variables were created from existing variables to streamline the number of variables in the analyses. Renal dysfunction was considered to be present for those who were undergoing dialysis or had elevated creatinine levels. And secondly, diabetes mellitus Types I and II were combined into a single variable due to the continually changing definitions of the types of this condition.

For those patients who were admitted with a diagnosis of acute myocardial infarction and who had a cardiac catheterization procedure performed on the same day as the PCI, a variable called 'direct procedure' was created.

The Duke Coronary Index is a measure of a patient's coronary anatomy and is assessed before and after the PCI procedure (Smith et al., 1991). (Also, refer to Appendix I for further explanation). In APPROACH, this index was recorded as a 14-category variable. To include it in the model building process in the original form would have been unmanageable and difficult to interpret. Therefore, two new variables were created to indicate the presence/absence of pre-PCI stenosis of the proximal left anterior descending (Prox. LAD) artery and of pre-PCI stenosis of the left main (Lft. Main) artery.

### *5.3.3 Missing data*

Missing data is a common challenge of a registry. In this dataset, a handful of variables were missing minor amounts of data. For example, one case was dropped from the study population because it was missing a value for the presence/absence of cardiogenic shock. Another 43 cases were



eliminated because they were missing data for pre- and post-PCI Duke Jeopardy Score and Duke Coronary Index.

Unfortunately, several key variables were missing a substantial amount of data (Table 5.2). The Canadian Cardiovascular Society (CCS) Angina Classification grades patients according to the severity of angina pectoris (Campeau 1976). This scale of increasing severity of angina presentation has been described in Appendix I. Unfortunately, 16.5% of the cases were missing data on this variable.

Table 5.2. Baseline characteristic variables with significant amounts of missing data (n=2751).

Variable	Value	Percent
CCS Angina Class	0	1.7
	I	2.0
	II	11.8
	III	11.7
	IV a	32.6
	IV b	8.0
	IV c	14.2
	Atypical	1.4
	Missing	16.5
Ejection Fraction	Not done	14.9
	<30%	2.0
	30-50%	15.4
	>50%	25.7
	Missing	42.1
Priority	Emergency	13.1
	Urgent In Patient	39.6
	Urgent Out Patient	6.2
	Planned	17.2
	Missing	23.9
IABP	No	89.6
	Yes	1.9
	Missing	8.5

CCS, Canadian Cardiovascular Society, IABP, intra-aortic balloon pump



Left ventricular ejection fraction is an indicator of left ventricular (dys)-function. These values were originally categorized into > 50%, 30-50%, < 30%, 'ventriculogram not done' due to instability of the patient. Again, there was a considerable amount of missing data (42.1%) for this variable. 'Priority' and 'IABP' variables also had a significant amount of missing data (23.9% and 8.5%, respectively).

Several strategies of dealing with the missing data were considered. Elimination of the cases with missing data is simple but inappropriate option, as it would drastically reduce the sample size (Greenland and Finkle 1995). Another option was to reclassify the cases with missing values into another category with similar outcomes. However, this option was not acceptable because the re-classification was dependent on the outcome. Imputation via nested regression models was a third option. Norris et al (2000) pointed out an overwhelming challenge of these methods. A stringent assumption of these methods is that data are missing completely at random, that is, whether or not a given variable is missing is entirely independent of the values of the other variables, and also independent of whether other variables are missing (Norris et al 2000). However, data were not missing at random in this dataset. In fact, data were missing consistently from site C. Since this was a clear violation of this assumption, cases with missing data were, instead, included in the analyses as its' own 'missing' category.

## 5.4 STATISTICAL ANALYSES

The following briefly outlines the analytical approaches taken to satisfy each objective of the current study.

Objective 1: To describe the use of abciximab in Alberta PCI patients.

- Patients were classified into low, moderate and high-risk strata and the use of abciximab was compared across risk-strata. Analyses



were performed to investigate the inter-institutional differences in its use. A description of the theory and methods used in the development of the logistic regression models is also included here. Objective 2: To compare risk-adjusted outcomes in Alberta PCI patients who received abciximab to those who did not receive this adjunct therapy.

- The logistic regression models constructed for each outcome generated values necessary for the development of the observed to expected (O/E) ratio which was used to risk-adjust the overall rate of the outcome. Hospital site differences also were anticipated and the risk-adjusted outcome rates were calculated for each hospital site.

All statistical analyses were performed using the SPSS® statistical software (version 10.0.1).

#### *5.4.1 Utilization Analyses*

The first objective of this study was to describe the utilization of abciximab in Alberta PCI patients. Descriptive analyses were performed to characterize its use: (1) percentage of PCI patients who received abciximab in the overall cohort, (2) percentage of patients who received abciximab at each of the three hospital sites, and (3) percentage of patients who received abciximab over each of the four quarters of 1999 at each hospital site.

The concept of risk was also introduced as part of the first objective. It was hypothesized that high-risk (of death or repeat revascularization) PCI patients would be most likely to receive abciximab. Two methods of defining risk were undertaken. In the first method, the predicted probabilities of dying or undergoing a revascularization procedure were ranked from lowest to highest, and then divided into three risk levels (hereafter known as the risk score): low, moderate and high. The predicted





probabilities for each patient were generated by logistic regression models, which were developed to predict the occurrence of death or repeat revascularization within one year of the first PCI. These models took into account baseline characteristics of the patients who underwent PCI that may predispose or protect them from the occurrence of the adverse event. The methods used in the development of these models are explained in the next section of this chapter.

The development of a risk index was the second method of risk definition considered. Several examples of risk indices such as the Charlson comorbidity score and the TIMI risk score can be found in the peer-reviewed literature (Charlson et al 1987, Morrow et al 2000). Using the same methodology as the TIMI index, a risk index was developed. The first step was to assign whole numbers or weights to corresponding odds ratios of the logistic regression models described above. If the odds ratio was statistically significant at  $\alpha < 0.05$  and was greater than 1 but less than 2, a weight of 1 was assigned. If the odds ratio was greater than or equal to 2 but less than 2.5, a weight of 2 was assigned. And finally, if the odds ratio was greater than or equal to 2.5, a weight of 3 was assigned. The sum of these scores generated an overall risk index for each patient. For example, if Patient #1 was over the age of 75 years, diabetic, hypertensive and was admitted with an acute myocardial infarction (AMI), her/his risk index would equal seven (7) (Table 5.3). Note that the presence of hypertension received a weight of zero (0) because it was not a statistically significant predictor of death. However, if Patient #2 was younger than 75 years and diabetic, her/his risk index would equal one (1).



Table 5.3. Hypothetical logistic regression model predicting death within one year of PCI and assigned weights for the risk index.

Variable	OR	p-value	Weight
Age (>75 years)	3.65	0.004	3
Diabetes	1.96	0.030	1
Hypertension	2.38	0.125	0
AMI	5.42	0.001	3

The risk indices were then grouped into three strata of risk (low, moderate and high). The rate of abciximab was then examined and compared across each risk stratum.

For each risk stratification method, the use of abciximab was determined for each risk stratum and the Pearson chi-square test (at  $\alpha=0.05$ ) was applied to assess statistically significant differences in the abciximab utilization between the risk strata. An association was considered clinically significant if the relative (risk) increase or reduction was  $\geq 25\%$  (moderately) and  $\geq 50\%$  (highly) (Sackett et al 1991).

Another important methodological detail was the use of two different models for each outcome. The first model was developed using this dataset but was not validated (and is hereafter referred to as the 'current model'). The second model was internally validated model using data on Alberta residents who underwent PCI between July 1, 1995 and December 31, 1997 (and is hereafter referred to as the 'Kaul' model) (Kaul 2000). The congruence of variable definitions was not a concern when applying a previously validated model to the population in the current study as the APPROACH investigators collected the data on both populations. These two approaches of risk stratification and logistic regression models were applied to determine the robustness of the results.



## Logistic Regression Models

The primary purpose in constructing a model is to express the relationship between an outcome and a set of predictor variables. With that in mind, it is also desirable to generate the best fitting and most streamlined model. Not only should it make sense statistically, but biological plausibility should also exist.

Logistic regression sets itself apart from linear regression models in that the outcome or dependent variable is binary or dichotomous (Hosmer and Lemeshow 1989). Death and repeat revascularization (re-PCI or CABG) within one-year of the index PCI are the binary outcomes of interest in the current study. The logistic model provides the log-odds of the outcome occurring for an individual with a specific set of predictor variables. The logit (or the log of odds) transformation of the multiple logistic model is given by the equation:

$$g(x) = \ln \left[ \frac{\pi(x)}{1 - \pi(x)} \right] = \beta_0 + \beta_1 x_1 + \dots + \beta_i x_i$$

where  $g(x)$  is the link function which provides the natural log odds of an event based on the collection of independent predictor variables ( $x_1 \dots x_i$  (i.e., patient and disease characteristics));  $\pi(x_i)$  is the probability of the outcome;  $\beta_0$  is a constant and  $\beta_1$  thru  $\beta_i$  are the slopes of the corresponding predictor variables (Hosmer and Lemeshow 1989).

The above equation seems fairly complicated and awkward to interpret into meaningful conclusions. However, the ratio of the log odds for the presence of the outcome ( $X_1$ ) to the log odds of its absence ( $X_0$ ), otherwise

$$\psi = \frac{\text{odds}X_1}{\text{odds}X_0} = \frac{e^{(\beta_0 + \sum \beta_i X_{1i})}}{e^{(\beta_0 + \sum \beta_i X_{0i})}} = e^{\sum_{i=1}^k \beta_i (X_{1i} - X_{0i})}$$



known as the odds ratio,  $\psi$ , produces an intuitively simple measure of association. The ease of its interpretation is one of the most attractive features of logistic regression, especially if the predictor variable is dichotomous. For example, the relationship between death (no/yes), the outcome, and diabetes mellitus (no/yes), the predictor variable, for this study's population is as shown in Table 5.4.

Table 5.4. Contingency table of death and diabetes in 2751 PCI patients.

	Dead	Alive	Total
Diabetes	27	533	560
No Diabetes	67	2124	2191
Total	94	2657	2751

When using SPSS® statistical software, the  $\beta$  generate is 0.474. This value is then used to calculate the odds ratio,  $OR=e^{\beta}=e^{0.474}=1.60$ . This indicates that those patients who have diabetes mellitus had a risk of death within one year 1.6 times that of patients who do not have diabetes mellitus.

Model Building Strategies

Two steps were taken when constructing the logistic regression models:

- 1. Univariate analyses;
- 2. Multivariate model construction.

*Univariate analyses*

The utility of univariate analysis is demonstrated early in the model building process, as it is the initial phase of variable selection towards the construction of the multivariate model.





For nominal and ordinal variables, univariate analyses were carried out using a contingency table of the outcome versus the  $k$  levels of the independent variable. The likelihood ratio chi-square test was used to identify differences between the groups compared (Hosmer and Lemeshow, 1989).

For the continuous variables, age and number of lesions that have more than 70% stenosis, the univariate relationships to the outcomes were tested using univariate logistic regression. To confirm this relationship, two-sample  $t$  tests were also used.

Biologically plausible interactions were also tested for statistical significance at the univariate level.

#### Multivariate model construction

Upon completion of the univariate analyses, variables with likelihood ratio  $p$ -values  $<0.25$  and those of biological importance were selected for entry into the multivariate model building stage (Hosmer and Lemeshow 1989). This entry cut point of 0.25 may seem rather liberal, however, the use of a more traditional cut-point such as 0.05 may be too harsh by excluding variables of known significance (Mickey and Greenland 1989).

Once the significant variables were selected, the backward stepwise method was used to arrive at the final model. In SPSS<sup>®</sup>, all the variables are entered into the logistic regression model and through a series of iterations, the most statistically significant variables remain in the model. In the current study, those variables with statistical significance at  $p < 0.10$  remained in the final model.



### Measures of model fit and discrimination

Following the construction of the model, its fit and discriminatory power were assessed. The most popular measure of the fit of a logistic regression model is the Hosmer-Lemeshow goodness-of-fit statistic ( $\hat{C}$ ). This test categorizes the probabilities of the event occurring predicted by the model into deciles of ascending risk. The statistic is arrived at by calculating the Pearson chi-square statistic from the  $2 \times g$  table of observed and estimated frequencies,

$$\hat{C} = \sum_{k=1}^g \frac{(o_k - n_k \bar{\pi}_k)^2}{n_k \bar{\pi}_k (1 - \bar{\pi}_k)}$$

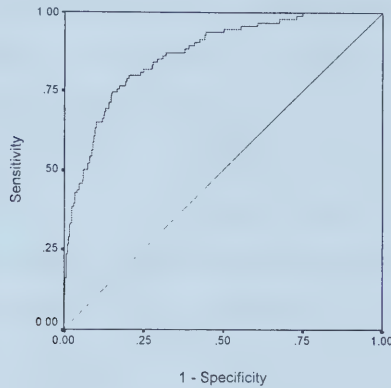
where  $g$ =deciles of risk=10,  $k=k^{\text{th}}$  decile,  $n_k$  is the total number of subjects in the  $k^{\text{th}}$  decile,  $o_k$  is the number of responses among  $c_k$  covariate patterns, and  $\bar{\pi}_k$  is the average estimated probability. Hosmer and Lemeshow demonstrated that when the fitted model is correct and when the number of distinct values of  $x$  observed ( $J$ ) equals the number of estimated probabilities ( $n$ ), the distribution of the goodness-of-fit statistic is nearly approximate to the chi-square distribution with  $g-2$  degrees of freedom (i.e.,  $df=10-2=8$ ). Based on this distribution, if the  $p$ -value is high (i.e., non-significant at  $\alpha=0.05$ ) then the model is said to fit the data well.

To assess a model's discriminatory power, the C-statistic was calculated as the area under the Receiver Operator Characteristic (ROC) curve (Hadorn et al 1992; Sackett et al 1991). Often this method has often been used to assess to the accuracy of diagnostic tools. However, this procedure can also be applied to evaluate the performance of the classification of patients into one of the two values of the outcome variable (i.e., alive/dead) (Miller, Hui, and Tierney 1991). As shown in the example



below (Figure 5.2), the ROC curve graphs the pairs of true positive rates (i.e., sensitivity rates) and false positive rates (i.e., 1-specificity).

Figure 5.2. An example of a ROC curve.



Ideally, the ROC curve would reside in the top left corner and the area under the curve would equal 1.0, which indicates that the model is perfect in identifying true events of the outcome. A model with no predictive ability would have an area of 0.5. Therefore, the larger the area under this curve, the greater confidence one would have in the model to correctly distinguish the patients at risk of dying or undergoing repeat revascularization from those who are not at risk. For example, the ROC curve in Figure 5.2 has an area of 0.868, which confers excellent discriminatory ability to that model.

#### *5.4.2 Risk Adjustment of Outcomes*

In light of the increasing focus on the performance and accountability of health care, risk adjustment is a popular tool used to evaluate the quality, value and outcomes of medical services. In general, risk adjustment attempts to account for factors that may explain variation in patient outcomes. Three factors may account for observed differences in



outcomes: differences in patient risk factors, random variation, or differences in the processes or structure of care (Daley 1994).

The primary interest of this study was to focus on the effect that abciximab had on clinical outcomes. To adjust for differences between patients who received abciximab and those who did not, logistic regression models predicting these outcomes were developed. Observed (O) versus expected (E) number of events of the outcomes (O/E) ratios were calculated for each treatment group (DeLong et al 1997, Iezzoni 1994). O/E ratios less than 1 indicated observed outcomes to be lower (better) than predicted; and conversely, O/E ratios greater than 1 indicated outcomes to be higher (poorer) than predicted. 95% confidence intervals surrounding the O/E ratio for each treatment population were calculated based on the normal approximation to the binomial distribution (DeLong et al 1997):

$$O \pm 1.96 \sqrt{\sum (p_i (1 - p_i))}$$

where O is the number of observed deaths and  $p_i$  is an individual's predicted probability of death. Then, the lower and upper values were divided by E, the number of expected deaths. The confidence intervals of the O/E ratio that did not include 1 were described as 'outliers' relative to the overall population. 'Outlier' status refers to the exclusion of 1.00 from the 95% CI of the O/E ratio. In other words, this method identifies which treatment group did significantly better (or worse) than the expected performance. If the 95% CI does not include 1.00 and is greater than 1.00, the site experienced more deaths than expected. If the 95% CI does not include 1.00 and is less than 1.00, the site experienced less death than expected. If the 95% CI does include 1.00, this indicates that the number of deaths observed are approximately equal to the number expected.





To calculate the risk-adjusted outcomes for each treatment group, the O/E ratio was multiplied by the overall population rate of the outcome. Finally, 95% confidence intervals for the risk-adjusted rates were determined by multiplying the lower and upper bounds of the 95% confidence intervals of the O/E ratio by the overall population mortality rate (Iezzoni 1994).

Hospital differences in the use of abciximab were suspected. Risk adjusted rates for each treatment group was then calculated for each hospital site.



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**CHAPTER 6: RESULTS: UTILIZATION OF ABCIXIMAB AND ITS EFFECT ON DEATH RATES WITHIN ONE YEAR OF THE INDEX PCI**

**6.1 INTRODUCTION**

The baseline characteristics of the 2751 patients undergoing PCI between January 7, 1999 and December 31, 1999 are presented in Tables 6.1a-f. (Abbreviations of terms are expanded at the end of Table 6.1f.) The mean age of the study population was  $62.2 \pm 11.6$  years, and 74.7% were men. Of the entire population, 1198 (43.5%) patients received abciximab while undergoing PCI in Alberta, and the overall death rate within one year of PCI was 3.42%.

**6.2 UTILIZATION OF ABCIXIMAB**

*Correlates of Abciximab Use*

The bivariate associations between the baseline characteristics and the use of abciximab are presented in the following tables. P-values of the likelihood ratio  $X^2$  test of these relationship are also presented and association were considered statistically significant at  $\alpha < 0.05$ . Among PCI patients who had received abciximab, there were greater numbers of men (than women) and patients who were younger than 75 years of age (than older than 75 years) (Table 6.1a). For the most part, comorbid conditions were not significantly associated with abciximab use. Only the frequencies of cerebrovascular disease and peripheral vascular disease were significantly lower in the patients who had received abciximab than those who did not.



Table 6.1a. Demographics and co-morbid conditions of the 2751 PCI patients, within which 1553 did not receive abciximab (no Abx) and 1198 did receive abciximab (Abx).

Characteristic		Overall (%) (n=2751)	No Abx (%) (n=1553)	Abx (%) (n=1198)	Abx Use (%)	p- value*
Sex	Male	74.7	73.2	76.5	44.6	0.046
	Female	25.3	26.8	23.5	40.3	
Age, mean (median) in Years		62.2 (62.7)	62.9 (63.5)	61.3 (61.5)		0.000
Age	< 75 years	84.7	83.0	86.9	44.7	0.005
	>= 75 years	15.3	17.0	13.1	37.3	
COPD	No	89.6	89.2	90.0	43.8	0.530
	Yes	10.4	10.8	10.0	41.8	
Cerebrovascular disease						0.001
		93.5	92.1	95.3	44.4	
		6.5	7.9	4.7	31.5	
Renal dysfunction						0.350
		97.2	97.4	96.8	43.4	
		2.8	2.6	3.2	48.7	
Dialysis	No	98.6	98.5	98.7	43.6	0.121
	Yes	1.4	1.5	1.3	41.0	
Diabetes (Types I and II)						0.496
		79.6	80.1	79.0	43.2	
		20.4	19.9	21.0	44.8	
Hyperlipidemia						0.121
		36.3	35.0	37.9	45.5	
		63.7	65.0	62.1	42.4	
Hypertension						0.381
		47.0	46.2	47.9	44.4	
		53.0	53.8	52.1	42.8	
Liver/GI disease						0.377
		95.6	95.3	96.0	43.7	
		4.4	4.7	4.0	39.7	
Malignancy						0.118
		96.0	95.5	96.7	43.8	
		4.0	4.5	3.3	36.4	
PVD	No	94.3	93.0	95.8	44.3	0.002
	Yes	5.7	7.0	4.2	31.6	
Present Smoker						0.449
		69.5	70.1	68.8	43.1	
		30.5	29.9	31.2	44.6	
Past Smoker						0.093
		62.1	60.7	63.9	44.8	
		37.9	39.3	36.1	41.5	

\*p-value of the Likelihood ratio  $X^2$  test.



Higher rates of abciximab use were associated with patients who had a history of congestive heart failure (CHF), prior myocardial infarction (MI), prior coronary artery bypass surgery (CABG) or prior thrombolytic therapy (Table 6.1b). However, those patients who had already undergone PCI prior to the index PCI did not receive abciximab as often as those undergoing PCI for the first time.

Table 6.1b. History of cardiac events.

Characteristic	Overall (%) (n=2751)	No Abx (%) (n=1553)	Abx (%) (n=1198)	Abx Use (%)	p- value*
History of CHF					0.042
No	87.2	88.3	85.7	42.8	
Yes	12.8	11.7	14.3	48.6	
Prior MI					0.000
No	35.6	40.6	29.0	35.6	
Yes	64.4	59.4	71.0	47.9	
Prior PCI					0.042
No	83.9	82.6	85.5	44.4	
Yes	16.1	17.4	14.5	39.2	
Prior CABG					0.005
No	90.2	91.6	88.4	42.7	
Yes	9.8	8.4	11.6	51.7	
Prior thrombolytic therapy					0.025
No	91.2	92.3	89.8	42.9	
Yes	8.8	7.7	10.2	50.4	

\*p-value of the Likelihood ratio  $\chi^2$  test.

A number of cardiac-specific variables measured upon admission were also significantly associated with higher rates of abciximab use: myocardial infarction upon admission, cardiogenic shock and advanced CCS angina classification (i.e., CCS $\geq$ III) (Table 6.1c).



Table 6.1c. Cardiac-specific characteristics presented upon admission.

Characteristic	Overall (%) (n=2751)	No Abx (%) (n=1553)	Abx (%) (n=1198)	Abx Use (%)	p- value*
MI on admission					0.000
No	53.4	62.7	41.3	33.7	
Yes	46.6	37.3	58.7	54.8	
Cardiogenic Shock					0.017
No	98.9	99.4	98.4	43.3	
Yes	1.1	0.6	1.6	65.5	
CCS Angina Class					0.000
0	1.7	2.1	1.3	31.3	
I	2.0	2.4	1.5	32.7	
II	11.8	16.3	6.0	22.2	
III	11.7	14.0	8.8	32.6	
IV a	32.6	33.2	31.9	42.5	
IV b	8.0	6.4	9.9	54.3	
IV c	14.2	9.5	20.2	62.1	
Atypical	1.4	1.5	1.3	38.5	
Missing	16.5	14.5	19.2	50.5	
CCS Angina Class					0.000
< III	33.5	36.8	29.2	38.0	
>= III	66.5	63.2	70.8	46.4	

\*p-value of the Likelihood ratio  $\chi^2$  test.

Among the indicators of coronary anatomy, patients having more than 2 lesions with greater than 70% stenosis, the presence of grafts, stenosis of the proximal left anterior descending artery or stenosis of the left main coronary artery were significantly associated with higher rates of abciximab use (Table 6.1d). However, left ventricular ejection fraction was not significantly associated with the use of this therapy.





Table 6.1d. Coronary anatomy.

Characteristic	Overall (%) (n=2751)	No Abx (%) (n=1553)	Abx (%) (n=1198)	Abx Use (%)	p- value*
#lesions >70% stenosis, mean (median)	2.27 (2.00)	2.16 (2.00)	2.41 (2.00)		0.000
# lesions >70% stenosis <= 2 lesions	67.2	69.6	64.2	41.6	0.003
>2 lesions	32.8	30.4	35.8	47.6	
Grafts					0.030
No	91.9	92.9	90.6	42.9	
Yes	8.1	7.1	9.4	50.4	0.017
Prox. LAD					
No	75.8	77.5	73.5	42.3	0.015
Yes	24.2	22.5	26.5	47.5	
Lft. Main disease					0.015
No	97.6	98.2	96.7	43.2	
Yes	2.4	1.8	3.3	58.2	0.671
LVEF					
V-gram not done	14.9	14.7	15.1	44.3	
<30%	2.0	2.1	2.0	42.9	
30-50%	15.4	16.2	14.4	40.7	
>50%	25.7	25.9	25.3	42.9	
Missing	42.1	41.1	43.2	44.8	

\*p-value of the Likelihood ratio  $X^2$  test.



Patients who were treated with an intra-aortic balloon pump (IABP) and stent(s) were more likely to receive abciximab than those not treated with these devices (Table 6.1e). Patients who presented with an acute myocardial infarction and underwent cardiac catheterization and PCI during the same day (i.e., ‘direct procedure’ variable) were also more likely to be treated with abciximab than those whose circumstances were not as urgent. A comparable association was also found in patients who were classified as ‘emergency’ cases.

Table 6.1e. Procedural characteristics.

Characteristic	Overall (%) (n=2751)	No Abx (%) (n=1553)	Abx (%) (n=1198)	Abx Use (%)	p- value*
Complete revascularization					0.408
No	47.5	48.2	46.6	42.7	
Yes	52.5	51.8	53.4	44.3	
Direct Procedure					0.000
No	68.0	75.5	58.4	37.4	
Yes	32.0	24.5	41.6	56.7	
Priority					0.000
Emergency	13.1	8.0	19.7	65.4	
Urgent In Patient	39.6	37.2	42.7	46.9	
Urgent Out Patient	6.2	6.6	5.7	40.0	
Planned	17.2	20.0	13.6	34.5	
Missing	23.9	28.2	18.4	33.4	
IABP					0.000
No	89.6	84.4	96.3	46.8	
Yes	1.9	0.5	3.7	84.6	
Missing	8.5	15.1	0.0	0.0	
Stent					0.000
No	15.3	19.8	9.5	27.1	
Yes	84.7	80.2	90.5	46.5	

\*p-value of the Likelihood ratio  $\chi^2$  test.

Notably, the use of abciximab was not significantly associated with the rates of death, (repeat) PCI, CABG, or any revascularization procedure (Table 6.1f).



Table 6.1f. Unadjusted outcomes.

Characteristic	Overall (%) (n=2751)	No Abx (%) (n=1553)	Abx (%) (n=1198)	Abx Use (%)	p- value*
Death w/in 1 year					0.056
No	96.6	97.2	95.8	43.2	
Yes	3.4	2.8	4.2	53.2	
Re-PCI w/in 1 year					0.859
No	86.3	86.4	86.2	43.5	
Yes	13.7	13.6	13.8	43.9	
CABG w/in 1 year					0.820
No	96.7	96.6	96.7	43.6	
Yes	3.3	3.4	3.3	42.4	
Any revasc. proc. w/in 1 year (CABG or re-PCI)					0.996
No	84.0	84.0	84.0	43.5	
Yes	16.0	16.0	16.0	43.5	

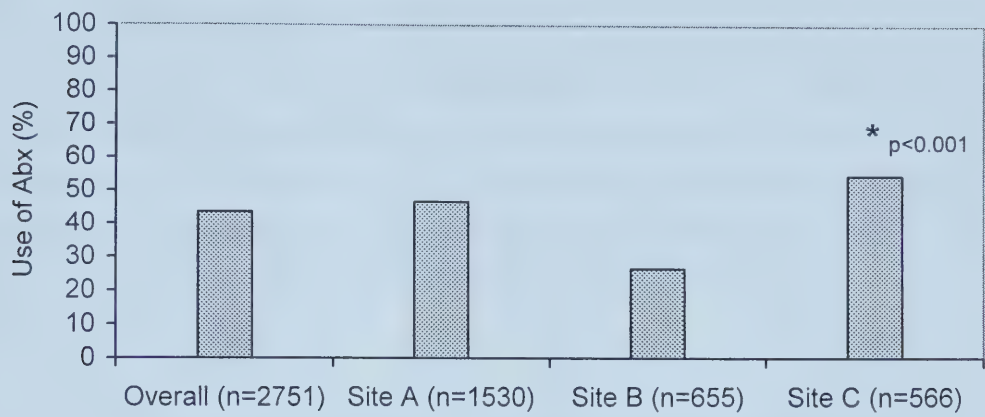
\*p-value of the Likelihood ratio  $\chi^2$  test. CABG (Coronary Artery Bypass Graft surgery); CCS (Canadian Cardiovascular Society); CHF (Congestive Heart Failure); COPD (Chronic Obstructive Pulmonary Disease); GI (Gastrointestinal Disease); IABP (Intra-Aortic Balloon Pump); Lft. Main (Left Main coronary artery); LVEF (Left Ventricular Ejection Fraction); MI (Myocardial Infarction); PCI (Percutaneous Coronary Intervention); proc.= procedure; Prox. LAD (Proximal Left Anterior Descending artery); PVD (Peripheral Vascular Disease); Re-PCI ((repeat) Percutaneous Coronary Intervention); revasc.=revascularization; V-gram (ventriculogram).

### *Hospital Site Differences*

The patients in the current study were treated at one of three cardiac catheterization sites in Alberta. Clinical practice guidelines regarding the use of abciximab with PCI have not been established regionally or provincially. And as such, inter-institutional differences were anticipated. As shown in Figure 6.1, there were significant differences across the sites ( $p<0.001$ ). These discrepancies seem to have been driven by the low rate of use (26.6%) at site B.

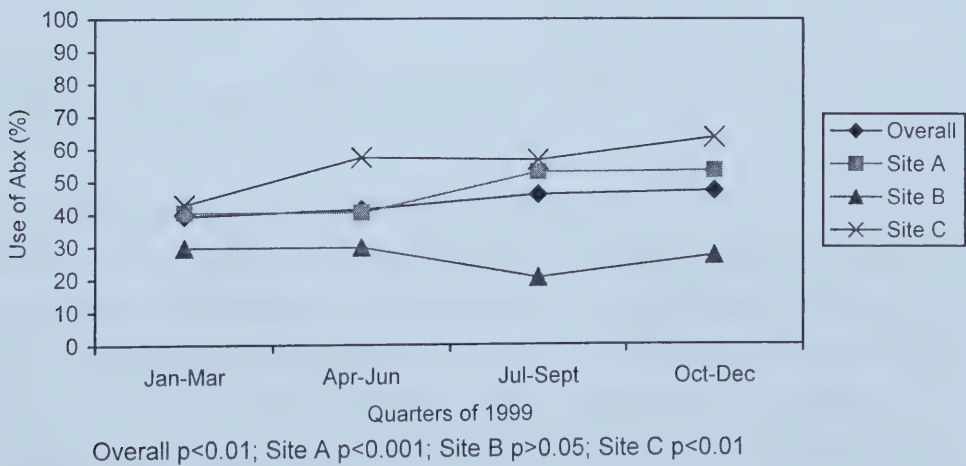


Figure 6.1. Utilization in the overall population (n=2751) and in each hospital site.



When the frequency of abciximab use was calculated for the four quarters of 1999, temporal variations were exposed (Figure 6.2). At the beginning of 1999 Sites A and C used this therapy in approximately 40% of patients. As the year progressed, their use of abciximab tended to climb. Site B's utilization of abciximab was consistently lower than the other sites during all four quarters, and even dipped in the third quarter.

Figure 6.2. Temporal trend of the use of abciximab during 1999.







To further characterize the use of abciximab during 1999, patients were stratified based on their risk of death within one year of the index PCI. As described in the previous chapter, two different approaches were taken. The first approach ranked the individual predicted probabilities generated by the logistic regression model and categorized patients into tertiles: low-, moderate- and high-risk strata. The use of this therapy was not associated with the risk strata based on the current model ( $p=0.914$ ) (Table 6.2a). This result held true when the Kaul model was applied to this population ( $p=0.584$ ) (Table 6.2b).

Table 6.2a. Utilization of abciximab according to risk strata. (Using the current model).

Risk level (no. of patients)	Observed Death(%)	Expected Death(%)	Abx Rate (%)
Low (917)	0.327	0.307	43.5
Moderate (917)	1.09	1.20	43.1
High (917)	8.83	8.74	44.1
Pearson $X^2$ test=0.180, $p=0.914$			

Table 6.2b. Utilization of Abciximab according to risk strata. (Using the Kaul model).

Risk level (no. of patients)	Observed Death(%)	Expected Death(%)	Utilization Rate (%)
Low (917)	0.327	0.393	43.0
Moderate (917)	1.53	1.38	42.7
High (917)	8.40	8.47	44.9
Pearson $X^2$ test=1.076 $p=0.584$			

At the institutional level, patterns of abciximab’s use were diverse. As Table 6.3a indicates, site B appeared to be selective in their administration of abciximab, with the high-risk group receiving it more often ( $p<0.01$ ). Relative to the low- and moderate-risk group, there was an increase in the use of abciximab of 52% and 50% in the high-risk group, respectively. In contrast, sites A and C seemed to administer this therapy most often to



patients at low risk, although this pattern did not reach statistical or clinical significance ( $p>0.25$  respectively; relative increases were less than 25%).

Table 6.3a. Utilization of Abciximab according to risk strata and hospital site. (Using the current model).

Hospital Site	Risk Level (no. of patients)	Observed Death(%)	Expected Death(%)	Abx rate (%)	X <sup>2</sup> p-value
A (1530)	Low (543)	0.000	0.294	49.2	0.256
	Moderate (512)	0.977	1.201	46.7	
	High (475)	7.37	8.47	44.0	
B (655)	Low (239)	0.837	0.314	22.6	0.007
	Moderate (200)	0.500	1.171	23.0	
	High (216)	9.72	10.1	34.3	
C (566)	Low (135)	0.741	0.350	57.8	0.696
	Moderate (205)	1.95	1.23	53.7	
	High (226)	11.1	7.43	53.5	

Interestingly, the tendency to administer of abciximab to low-risk patients at Site A became statistically significant when the Kaul model was used ( $p<0.05$ ) (Table 6.3b). In addition, the pattern at Site C changed when the Kaul model was applied. Patients at highest and lowest risk received abciximab most often, even though this relationship did not reach statistical or clinical significance ( $p>0.05$ ).

Table 6.3b. Utilization of Abciximab according to risk strata and hospital site. (Using the Kaul model).

Hospital Site	Risk Level (no. of patients)	Observed Death(%)	Expected Death(%)	Abx rate (%)	X <sup>2</sup> p-value
A (1530)	Low (500)	0.200	0.390	51.0	0.017
	Moderate (519)	0.963	1.39	47.2	
	High (511)	6.65	8.53	42.1	
B (655)	Low (286)	0.350	0.378	22.4	0.003
	Moderate (188)	2.13	1.32	23.9	
	High (181)	10.0	10.4	35.9	
C (566)	Low (131)	0.769	0.436	57.3	0.084
	Moderate (210)	2.38	1.43	48.6	
	High (225)	11.0	15.3	58.7	



The second method of risk stratification, the risk index, assigned whole numbers to significant predictors of the adverse outcome (i.e., odds ratio > 1.0) and a cumulative risk index was generated for each patient. The risk index was then amalgamated into three levels of risk: low, moderate and high (Figure 6.3, 6.4, 6.5 and 6.6).

Figure 6.3. Death rate for each cumulative risk index (using the current model).

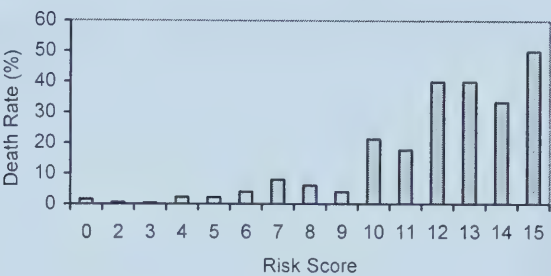
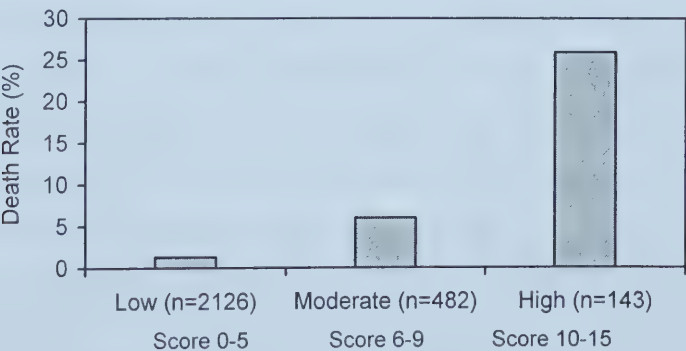


Figure 6.4. Amalgamation of risk index into low-, moderate- and high-risk strata (using the current model).



A similar classification of patients was developed when the Kaul model was applied (Figure 6.5 and 6.6).



Figure 6.5. Death rate for each cumulative risk index (using the Kaul model).

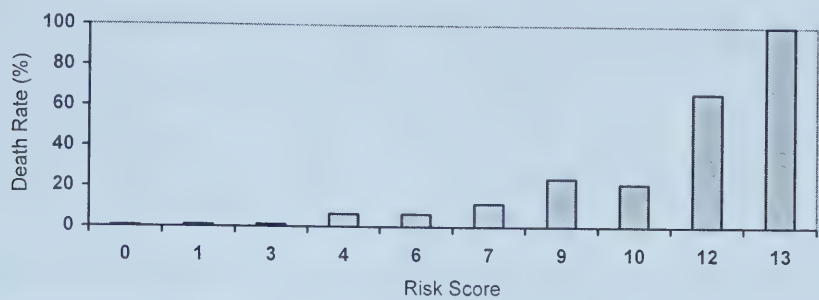
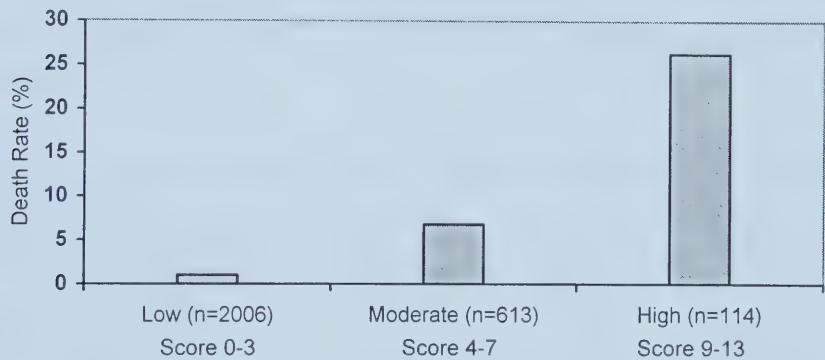


Figure 6.6. Amalgamation of risk index into low-, moderate- and high-risk strata (using the Kaul model).



In the overall population, the patients at high-risk of death tended to receive abciximab more often (Tables 6.4a and 6.4b). The relationship reached statistical significance only when the Kaul model was applied. Notably, there was a 30% increase in the use of abciximab in high-risk patients relative to the low-risk group (Table 6.4b).

Table 6.4a. Utilization of Abciximab by risk level (using the current model).

Risk Level (no. of patients)	Observed Death(%)	Expected Death(%)	Abx Rate (%)
Low (2126)	1.32	1.44	42.8
Moderate (482)	6.00	6.14	44.2
High (143)	25.9	23.7	52.4

Pearson  $\chi^2$  test=5.168,  $p=0.077$ .





Table 6.4b. Utilization of abciximab according to risk level (using the Kaul model).

Risk Level (no. of patients)	Observed Death(%)	Expected Death(%)	Abx Rate (%)
Low (2006)	1.05	1.33	41.3
Moderate (631)	6.80	6.04	49.1
High (114)	26.3	25.7	52.6

Pearson  $X^2$  test=16.03,p=0.000

In terms of inter-institutional differences, the use of abciximab was associated with the level of risk. Specifically, sites B and C tended to administer abciximab to those patients at highest risk (Table 6.5a). At Site B there was a 54% increase in abciximab use in the high-risk group relative to the low-risk group, and a 21% increase when compared to the patients at moderate risk.

Table 6.5a. Utilization of Abciximab by risk level and by hospital site (using current model).

Hospital Site	Risk Level (no. of patients)	Observed Death(%)	Expected Death(%)	Abx rate (%)	$X^2$ p-value
A (1530)	Low (1165)	0.944	1.31	49.6	0.000
	Moderate (277)	4.70	5.00	37.2	
	High (88)	18.2	21.4	38.6	
B (655)	Low (555)	1.08	1.52	22.9	0.000
	Moderate (77)	9.09	10.9	37.7	
	High (23)	47.8	40.9	78.3	
C (566)	Low (406)	2.71	1.68	50.5	0.005
	Moderate (128)	7.00	5.76	63.3	
	High (32)	31.3	17.53	71.9	

The relationship at Site A was altered when the Kaul model was used (Table 6.5b). Instead of the patients at moderate risk receiving abciximab least often, this risk group received this agent more often than the other groups. However, this relationship did not achieve statistical or clinical significance across the risk strata (Table 6.5b).



Sites B and C retained similar patterns of utilization and levels of statistical and clinical significance (Table 6.5b.). At site B, there was a 155% increase of abciximab use in high-risk patients relative to the patients at low risk, and a 76% relative increase compared to moderate-risk patients. At site C, the use of abciximab increased 48% and 32% in high-risk patients relative to low-risk and moderate-risk patients, respectively.

Table 6.5b. Utilization of abciximab according to risk level and hospital site (using the Kaul model).

Hospital Site	Risk Level (no. of patients)	Observed Death(%)	Expected Death(%)	Abx rate (%)	$\chi^2$ p-value
A (1530)	Low (1078)	0.853	1.29	45.7	0.355
	Moderate (392)	5.60	5.79	50.8	
	High (60)	15.0	26.8	38.3	
B (655)	Low (507)	0.593	1.09	22.9	0.000
	Moderate (117)	8.53	6.96	32.5	
	High (31)	35.5	27.9	64.5	
C (566)	Low (421)	2.14	1.71	52.0	0.022
	Moderate (122)	9.03	5.96	59.8	
	High (23)	43.5	19.5	73.9	

*Summary*

Overall, the rate of abciximab use seemed to be highest in the patients who were at greatest risk of death within one year of PCI (Table 6.6). However, only one method yielded a statistically significant relationship. When both the Kaul model and the risk index were applied, the use of abciximab increased significantly as the severity of the risk of death increased ( $p<0.001$ ).



Table 6.6 Summary of utilization patterns with respect to the risk stratification method and logistic regression model predicting death used.

Risk Stratification Method	Model	
	Current Model	Kaul Model
Risk Score	* ; NS	* ; NS
Risk index	+ ; NS	+ ; S

'+' indicates an increasing trend in use as the severity of risk increases; '\*' indicates mixed utilization pattern; NS=not statistically significant; S=statistically significant.

At the hospital level, there was little consistency in the patterns within sites A and C (Table 6.7). Yet, utilization patterns at Site B indicated that high-risk patients received abciximab more often, regardless of the model or risk stratification method applied.

Table 6.7. Summary of utilization patterns across the three hospital sites with respect to the risk stratification method and logistic regression model predicting death used.

Risk Stratification Method	Site A		Site B		Site C	
	Current	Kaul	Current	Kaul	Current	Kaul
Risk score	- ;NS	- ;S	+ ;S	+ ;S	- ;NS	*; NS
Risk index	* ;S	* ;NS	+ ;S	+ ; S	+ ;S	+ ;S

'+' indicates an increasing trend in use as the severity of risk increases; '-' indicates a decreasing trend in use as the severity of risk increases; '\*' indicates mixed utilization pattern; NS=not statistically significant; S=statistically significant.

### 6.3 RISK-ADJUSTED DEATH RATES

To determine the effect of the abciximab in these PCI patients, risk-adjusted rate of death within one year of the index PCI was calculated for users and non-users of abciximab. Two different logistic regression models have been used to predict the occurrence of death. The first being a current model constructed for this population, and the second, the Kaul model which was developed on patients undergoing PCI from 1995 to 1997 in the APPROACH database (see Appendix II for final models). Both models were used to calculate the risk-adjusted death rates.



In Tables 6.8a and 6.8b, the risk-adjusted death rates are presented for those who did received abciximab as an adjunct to PCI and for those who did not receive this therapy. A set of risk-adjusted death rates was also calculated for each hospital sites.

On first glance, the risk-adjusted death rates are comparable between the models. This similarity was expected as the two models share similar c-index statistics and Hosmer-Lemeshow goodness-of-fit statistics (see Appendix II).

At the outset of the study, it was hypothesized that abciximab was be effective in reducing death rates. As Tables 6.8a and 6.8b show, the differences in death rates were not statistically significant between users and non-users of abciximab. However, the difference in death rates at Site B may be clinically significant as the use of abciximab produced a relative risk increase of over 43% (Tables 6.8a and 6.8b).

Table 6.8a. Risk-adjusted death rates by abciximab use and hospital site (using the current model).

Abx Use	Observed Death Rate (%)	Expected Death Rate (%)	O/E Ratio	Risk-adjusted Death Rate (%)	95%CI of Risk- adjusted Death Rate
<i>Overall</i>					
No (1553)	2.83	3.10	0.914	3.13	(2.25, 4.01)
Yes (1198)	4.17	3.83	1.089	3.72	(2.85, 4.60)
<i>Site A</i>					
No (815)	2.70	3.26	0.829	2.84	(1.67, 4.00)
Yes (715)	2.52	3.00	0.840	2.87	(1.58, 4.16)
<i>Site B</i>					
No (481)	2.08	2.80	0.743	2.54	(0.856, 4.22)
Yes (174)	8.05	7.32	1.100	3.76	(2.22, 5.30)
<i>Site C</i>					
No (257)	4.67	3.14	1.489	5.09	(2.85, 7.34)
Yes (309)	5.83	3.80	1.536	5.25	(3.45, 7.05)

Abx, abciximab; CI, confidence interval; O/E, observed versus expected





Figure 6.7. Risk-adjusted death rates in the overall population (n=2751), site A (n=1530), site B (n=655) and site C (n=566) (using the current model).

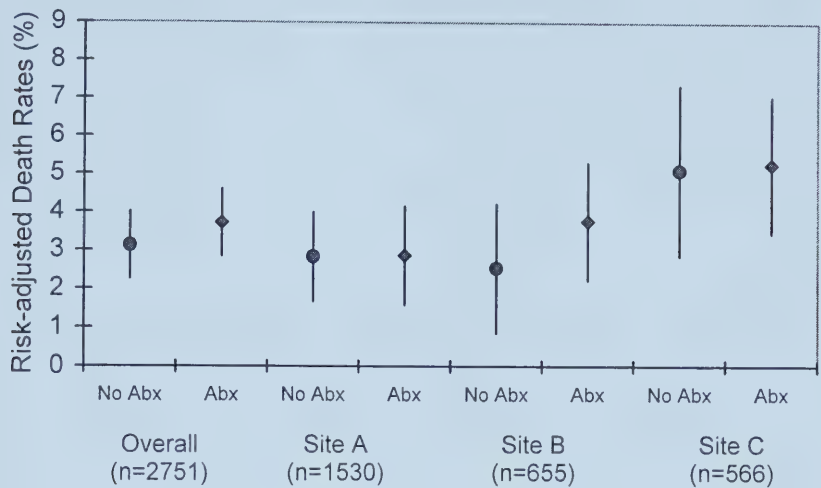


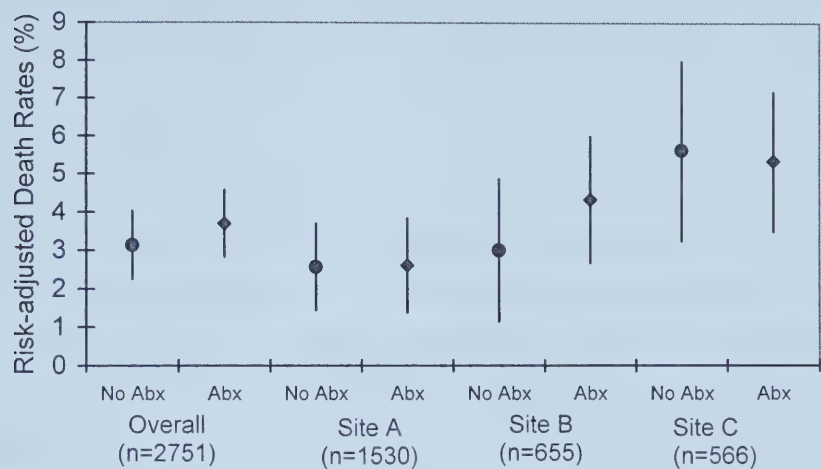
Table 6.8b. Risk-adjusted death rates by abciximab use and by hospital site (using the Kaul model).

Abx Use	Observed Death Rate (%)	Expected Death Rate (%)	O/E Ratio	Risk-adjusted Death Rate (%)	95%CI of Risk-adjusted Death Rate
<b>Overall</b>					
No (1553)	2.83	2.84	0.911	3.12	(2.25, 4.04)
Yes (1198)	4.17	3.74	1.114	3.81	(2.83, 4.58)
<b>Site A</b>					
No (815)	2.70	3.59	0.752	2.57	(1.44, 3.71)
Yes (715)	2.52	3.29	0.766	2.62	(1.38, 3.85)
<b>Site B</b>					
No (481)	2.08	2.36	0.881	3.01	(1.15, 4.88)
Yes (174)	8.05	6.35	1.267	4.33	(2.67, 6.00)
<b>Site C</b>					
No (257)	4.67	2.84	1.642	5.62	(3.23, 7.99)
Yes (309)	5.83	3.74	1.558	5.33	(3.48, 7.17)

Abx, abciximab; CI, confidence interval; O/E, observed versus expected.



Figure 6.8. Risk adjusted death rates for the overall population (n=2751), site A (n=1530), site B (n=655) and site C (n=566). (Using Kaul model.)





**Chapter 7: Results: UTILIZATION OF ABCIXIMAB AND ITS EFFECT ON REVASCULARIZATION RATES WITHIN ONE YEAR OF THE INDEX PCI**

**7.1 INTRODUCTION**

The second outcome of interest was the rate of revascularization within one year of the index PCI. To maintain consistency with the methodology of the Kaul model, patients who were alive upon discharge from the index hospitalization were included in the following analyses (Kaul 2000). In addition, those who had died within one year without undergoing a revascularization procedure were eliminated from the study population. Overall, 86 patients (3.1%) were eliminated, which left 2665 patients eligible for this analysis. Of the 2665 patients, 1152 (43.2%) received abciximab and 434 (16.3%) underwent a revascularization procedure within one year of the index PCI.

**7.2 UTILIZATION OF ABCIXIMAB AND THE RISK OF REVASCULARIZATION**

In general, patients who were considered to be at lowest risk of revascularization within one year received abciximab more often than those who were at higher risk (Tables 7.1a and 7.1b). This trend was statistically significant when the current model was used to predict the occurrence of revascularization, however, it was not when the Kaul model was applied.

Table 7.1a. Utilization of abciximab by risk level using the current model.

Risk level	Observed Revasc. Rate (%)	Expected Revasc. Rate (%)	Abx Rate (%)
Low (888)	8.59	9.25	46.8
Moderate (888)	14.3	14.6	44.2
High (889)	25.8	24.9	38.6

Pearson  $X^2$  test=12.653, p=0.002



Table 7.1b. Utilization of abciximab by risk level using the Kaul model.

Risk level (no. of patients)	Observed Revasc. Rate (%)	Expected Revasc. Rate (%)	Abx Rate (%)
Low (953)	10.4	11.2	45.8
Moderate (844)	16.2	15.7	42.0
High (868)	22.8	22.3	41.6

Pearson  $\chi^2$  test=3.938 p=0.140

Risk was also dichotomized into low- and high-risk levels for reasons that will become evident later in this chapter. Regardless of the model used, those patients who received abciximab more often were at lower risk of revascularization ( $p<0.05$ ) (Tables 7.2a and 7.3b). However, clinically significant differences between the risk strata were not observed.

Table 7.2a. Utilization of abciximab by dichotomous risk score using the current model.

Risk level	Observed Revasc. Rate (%)	Expected Revasc. Rate (%)	Abx Rate (%)
Low (1332)	11.1	10.6	45.6
High (1333)	21.4	21.9	40.8

Pearson  $\chi^2$  test= 6.367 p=0.012

Table 7.2b. Utilization of abciximab by dichotomous risk score using the Kaul model.

Risk level	Observed Revasc. Rate (%)	Expected Revasc. Rate (%)	Abx Rate (%)
Low (1321)	11.1	12.1	46.2
High (1344)	21.3	20.4	40.3

Pearson  $\chi^2$  test=9.382 p=0.002

### *Hospital site differences*

At Site A, abciximab was most often administered to patients who were at lowest risk of revascularization, and this relationship achieved statistical significance when the Kaul model was used. Patients at Site C who were at moderate risk tended to receive abciximab most often but this relationship





was not statistically or clinically significant. Patterns at Site B differed depending on the model applied.

Table 7.3a. Utilization of abciximab by risk level and hospital site using the current model.

Hospital Site	Risk Level (no. of patients)	Observed Revasc. (%)	Expected Revasc. (%)	Abx Rate (%)	X <sup>2</sup> p-value
A (1492)	Low (534)	7.1	9.1	48.7	0.232
	Moderate (515)	11.1	14.6	47.7	
	High (443)	21.5	23.3	43.4	
B (635)	Low (145)	14.5	9.6	26.9	0.809
	Moderate (203)	20.9	14.6	23.9	
	High (287)	30.9	27.5	25.6	
C (538)	Low (207)	8.3	9.3	55.8	0.193
	Moderate (172)	16.4	14.6	57.9	
	High (159)	28.9	24.9	48.4	

Table 7.3b. Utilization of abciximab by risk level and by hospital site using the Kaul model.

Hospital Site	Risk Level (no. of patients)	Observed Revasc. Rate (%)	Expected Revasc. Rate (%)	Abx rate (%)	X <sup>2</sup> p-value
A (1492)	Low (537)	7.45	11.3	51.8	0.015
	Moderate (432)	10.9	15.6	44.4	
	High (523)	19.7	22.3	43.6	
B (635)	Low (227)	18.9	11.2	23.8	0.539
	Moderate (230)	27.2	15.9	24.6	
	High (178)	26.1	22.3	28.4	
C (538)	Low (189)	8.47	11.5	55.0	0.265
	Moderate (183)	14.9	15.8	58.0	
	High (166)	28.9	22.5	54.3	

When risk was dichotomized, there was slightly better consistency between the current and Kaul models (Table 7.4a). Patients at sites A and C administered abciximab most often to those at low-risk, though this relationship only achieved statistical and clinical significance in Site A when the Kaul model was applied ( $p < 0.001$ , 25% relative increase in use). The



utilization of abciximab was homogeneous across the risk strata in Site B, regardless of the model applied.

Table 7.4a. Utilization of abciximab by dichotomous risk score and by hospital site using the current model.

Hospital Site	Risk Level (no. of patients)	Observed Revasc. Rate (%)	Expected Revasc. Rate (%)	Abx rate (%)	X <sup>2</sup> p-value
A (1492)	Low (792)	9.2	10.5	48.0	0.299
	High (700)	16.7	20.1	45.4	
B (635)	Low (248)	17.9	11.2	25.2	0.944
	High (387)	27.8	24.4	25.5	
C (538)	Low (292)	10.7	10.4	56.4	0.295
	High (246)	24.5	21.7	51.8	

Table 7.4b. Utilization of abciximab by dichotomous risk scores and by hospital site using the Kaul model.

Hospital Site	Risk Level (no. of patients)	Observed Revasc. Rate (%)	Expected Revasc. Rate (%)	Abx rate (%)	X <sup>2</sup> p-value
A (1492)	Low (724)	7.8	11.9	52.1	0.000
	High (768)	17.5	20.5	41.7	
B (635)	Low (329)	20.5	12.2	24.2	0.473
	High (306)	27.6	20.2	26.6	
C (538)	Low (270)	8.9	12.3	56.9	0.228
	High (268)	25.1	20.4	51.7	

### *Risk index*

Due to the small number of predictors of repeat revascularization, the range of the risk index was limited. This was particularly true in the Kaul model, which contained only one predictor, '>2 lesions with >70% stenosis', with an odds ratio greater than one. Therefore, individuals were automatically categorized into low- or high-risk levels. Figures 7.1 to 7.3 summarize the crude risk index and its amalgamation into two levels of risk.



Figure 7.1. Distribution of risk index developed from the current risk model.

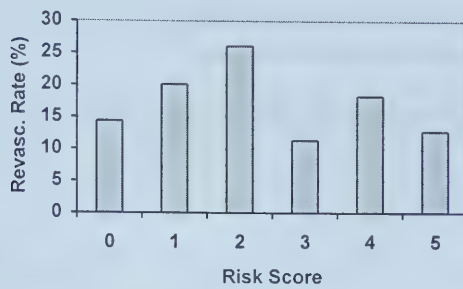


Figure 7.2. Amalgamated risk index (based on the current model).

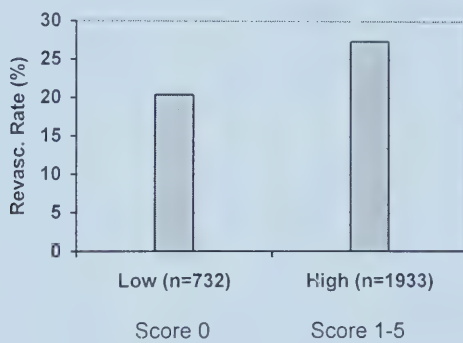
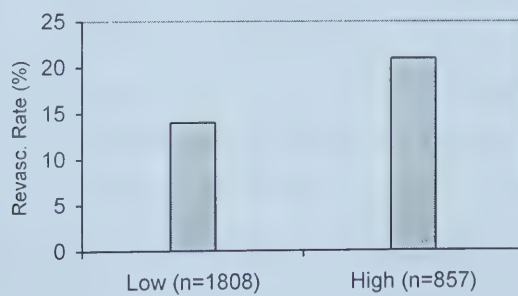


Figure 7.3. Risk index derived from the Kaul model.



When risk was defined according to the risk index, the utilization patterns were quite different from those determined by the previous risk stratification method. Instead of the low risk group receiving abciximab more often, administration of abciximab occurred most often in patients at high-risk of



revascularization ( $p<0.010$ ) (Table 7.5a and 7.5b). In fact, there was a 57% increase in use in the high-risk patients relative to those at low risk (Table 7.5a).

Table 7.5a. Utilization of abciximab by risk level using the current model.

Risk level	Observed Revasc. Rate (%)	Expected Revasc. Rate (%)	Abx Rate (%)
Low (732)	14.4	15.1	30.6
High (1933)	16.9	16.7	48.0

Pearson  $X^2$  test=64.616  $p=0.000$

Table 7.5b. Utilization of abciximab by risk level using the Kaul model.

Risk level	Observed Revasc. Rate (%)	Expected Revasc. Rate (%)	Abx Rate (%)
Low (1808)	14.0	14.0	41.4
High (857)	20.9	20.9	47.1

Pearson  $X^2$  test=7.872  $p=0.005$

*Hospital site differences*

At each hospital site, patients at highest risk of revascularization tended to receive abciximab most often (Table 6.6a and 6.6b). This relationship achieved statistical significance at every site and clinical significance at Sites A and B when the current model was applied. The use of abciximab was associated with a 57% increase in high-risk patients relative to those at low risk in Site A. Site B had a 94% increase in the use of abciximab in the high-risk group relative to those at low risk. However, the differences in utilization between risk strata at Sites A and C were not statistically or clinically significant when the Kaul model was used (Table 6.6b).

Table 7.6a. Utilization of abciximab by risk level and by hospital site using the current model.

Hospital Site	Risk Level (no. of patients)	Observed Revasc. Rate (%)	Expected Revasc. Rate (%)	Abx rate (%)	$X^2$ p-value
A (1492)	Low (332)	9.67	14.2	32.0	0.000
	High (1160)	13.6	15.5	51.0	
B (635)	Low (234)	23.7	17.2	15.9	0.000
	High (401)	24.1	20.5	30.8	
C (538)	Low (166)	10.9	14.2	48.5	0.044
	High (372)	19.7	16.2	56.9	





Table 7.6b. Utilization of abciximab by risk level and hospital site using the Kaul model.

Hospital Site	Risk Level (no. of patients)	Observed Revasc. Rate (%)	Expected Revasc. Rate (%)	Abx rate (%)	X <sup>2</sup> p-value
A (1492)	Low (976)	10.1	13.8	45.7	0.249
	High (516)	17.7	21.2	48.8	
B (635)	Low (470)	23.7	14.5	23.3	0.043
	High (165)	24.5	20.4	31.3	
C (538)	Low (361)	11.9	14.1	53.1	0.412
	High (177)	27.3	21.0	56.8	

*Summary*

The results of the two methods of risk stratification presented in the current study differ dramatically (Table 7.7). If one compares the results of the dichotomous risk stratification in the overall population, the risk score uncovered a trend of increased use of abciximab in the low-risk group. Conversely, the risk index yielded a trend of increasing abciximab use in the high-risk group.

Table 7.7. Summary of utilization patterns with respect to the risk stratification method and logistic regression model predicting revascularization used.

Risk Stratification Method	Model	
	Current Model	Kaul Model
Risk score	- ;S	- ;NS
Dichotomous Risk Score	- ;S	- ;S
Risk index	+ ;S	+ ;S

'+' indicates an increasing trend in use as the severity of risk increases; '-' indicates a decreasing trend in use as the severity of risk increases; '\*' indicates mixed utilization pattern; NS=not statistically significant; S=statistically significant.

When the patients were stratified by hospital site, the sensitivity of the risk stratification methods became even more apparent (Table 7.8). Generally, there seemed to be homogeneity in abciximab use across risk strata in most hospitals when the risk score was applied. Only when the Kaul model



was used did Site A emerge with a distinct pattern of using abciximab most often in low-risk patients ( $p<0.001$ ) (Table 7.8). In contrast, all hospital sites seemed to be using abciximab more often in the high-risk patients when the risk index was applied to the current model. This relationship became statistically significant only in Site B when the Kaul model was used, whereas the utilization patterns at Sites A and C were not statistically significant.

Table 7.8. Summary of utilization patterns across the three hospital sites with respect to the risk stratification method and logistic regression model predicting revascularization used.

	Site A		Site B		Site C	
Risk Stratification Method	Current	Kaul	Current	Kaul	Current	Kaul
Risk score	- ;NS	- ;S	* ;NS	+ ;NS	* ;NS	* ;NS
Dichotomous Risk Score	- ;NS	- ;S	* ;NS	+ ;NS	- ;NS	- ;NS
Risk index	+ ;S	+ ;NS	+ ;S	+ ; S	+ ;S	+ ;NS

‘+’ indicates an increasing trend in use as the severity of risk increases; ‘-’ indicates a decreasing trend in use as the severity of risk increases; ‘\*’ indicates mixed utilization pattern; NS=not statistically significant; S=statistically significant.

### 7.3 RISK-ADJUSTED REVASCULARIZATION RATES

The effect of abciximab in this population was expected to reduce the risk-adjusted rates of revascularization in the patients who received this agent (Table 7.9a and 7.9b). Figures 7.4 and 7.5 display these results graphically. In the overall population, it appears that the administration of abciximab had no significant impact on the rates of revascularization. At the hospital site level, neither statistically or clinically significant differences were observed.



Table 7.9a. Risk-adjusted revascularization rates using the current model.

Abx Use	Observed Revasc. Rate (%)	Expected Revasc. Rate (%)	O/E Ratio	Risk-adjusted Revasc. Rate (%)	95%CI of Risk- adjusted Revasc. Rate
<i>Overall</i>					
No (1513)	16.17	16.76	0.965	15.73	13.94, 17.51
Yes (1152)	16.38	15.60	1.050	17.12	14.98, 19.25
<i>Site A</i>					
No (795)	11.98	15.57	0.769	12.50	9.95, 15.14
Yes (697)	13.63	14.83	0.919	14.98	12.13, 17.84
<i>Site B</i>					
No (473)	22.93	19.13	1.199	19.54	16.63, 22.45
Yes (162)	26.88	19.68	1.366	22.27	17.44, 27.08
<i>Site C</i>					
No (245)	16.73	16.09	1.040	16.95	12.44, 21.47
Yes (293)	17.18	15.20	1.131	18.43	14.11, 22.75

Abx, abciximab; CI, confidence interval; O/E, observed versus expected.

Figure 7.4. Risk-adjusted revascularization rates using the current model.

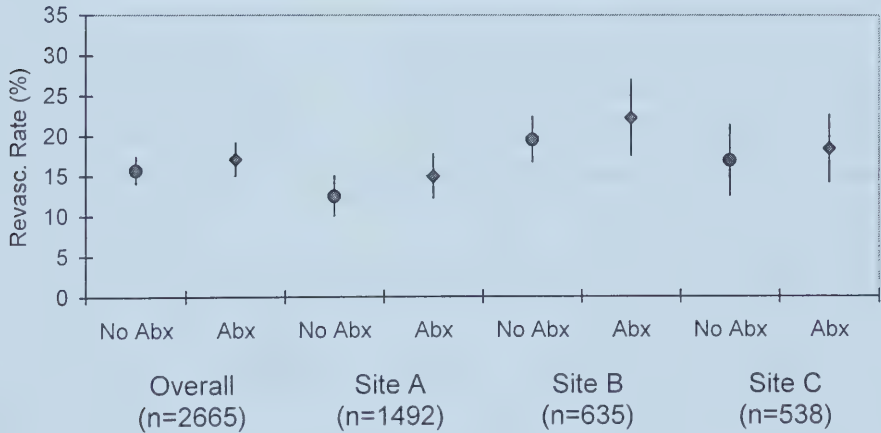


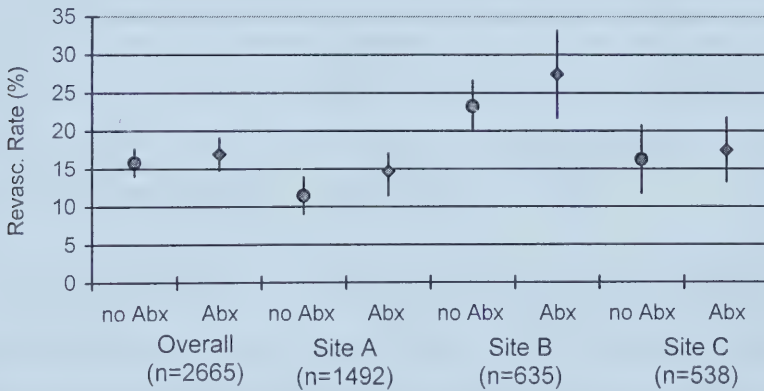


Table 7.9b. Risk-adjusted revascularization rates using the Kaul model.

Abx Use	Observed Revasc Rate (%)	Expected Revasc. Rate (%)	O/E Ratio	Risk-adjusted Revasc. Rate (%)	95%CI of Risk- adjusted Revasc. Rate
<b>Overall</b>					
No (1513)	16.17	16.66	0.971	15.38	14.02, 17.67
Yes (1152)	16.38	15.74	1.041	16.69	14.77, 19.09
<b>Site A</b>					
No (795)	11.98	16.98	0.705	11.50	9.02, 13.98
Yes (697)	13.63	15.58	0.875	14.26	11.47, 17.05
<b>Site B</b>					
No (473)	22.93	16.05	1.429	23.29	19.96, 26.63
Yes (162)	26.88	15.94	1.683	27.50	21.74, 33.24
<b>Site C</b>					
No (245)	16.73	16.77	0.998	16.27	11.77, 20.77
Yes (293)	17.18	16.01	1.073	17.49	13.24, 21.75

Abx, abciximab; CI, confidence interval; O/E, observed versus expected.

Figure 7.5. Risk-adjusted revascularization rates using the Kaul model.







## CHAPTER 8: DISCUSSION

### 8.1 SUMMARY OF RESULTS

Overall, 43.5% of Alberta residents who underwent their first PCI procedure during 1999 received abciximab. Of the three cardiac catheterization sites in Alberta, Site C had the highest utilization rate at 54.6%, while Site B administered abciximab the least (26.6%). Site B had a utilization rate of 46.7%. Reasons for this variation are likely multifactorial and include: prior experience in clinical trials with abciximab, patient selection, differing attitudes towards cost-containment and the absence of provincial clinical practice guidelines.

Overall, there was a tendency for higher abciximab use to be associated with a greater severity in the risk of death (when the risk index was used). However, this pattern was statistically and clinically significant only when the Kaul model was applied. When the risk score was applied, abciximab use was not associated with levels of risk.

Institutional utilization patterns were also examined. For Site B, high use of abciximab was associated with higher levels of risk, regardless of risk method or model applied. Utilization patterns of abciximab at Sites A and C varied depending on the methods employed.

Patients at low risk of revascularization tended to receive abciximab more often than those at high risk (when the risk score was used). An opposite pattern was revealed when the risk index was applied. Within hospital sites, patients at Sites A and C tended to follow the same patterns as the overall population. At Site B, there was a tendency for higher utilization of abciximab to be associated with higher risk patients, even though this



pattern only achieved statistical significance when the risk index method was applied.

In general, the results were not robust and differed considerably depending on the risk stratification technique and logistic regression model used. The Kaul model has the advantage of being internally validated via the data-splitting technique on a similar group of patients (Harrelet al 1996).

However, the application of this model to the present population may be somewhat problematic given other changes in treatment (e.g., greater use of stents). With regard to the risk stratification methods, the risk score is preferable to the risk index. The assignment of the risk index is relatively arbitrary as whole-numbered values are assigned to significant predictors of adverse outcomes (i.e., predictors with an odds ratio greater than one). Whereas the division of risk by rank-ordered predicted probabilities (i.e. tertiles) applies the actual odds ratios of all significant predictors.

Overall, there was no statistical difference between the two treatment groups in their risk-adjusted rates of death or revascularization. The risk-adjusted rates also did not significantly differ within each hospital site.

## 8.2 COMPARISON TO OTHER STUDIES

A handful of observational studies have emerged recently in attempts to clarify the utilization of abciximab in usual clinical practice. Similar to the hypothesis of the current study, these studies acknowledge that this agent has been reserved for high-risk patients in hopes of restraining costs (Lucore et al 2001, Velianou et al 2000, Plucinski et al 2000, Weiss et al 1999). However, none of these studies have defined 'high-risk' by the same methods as the current study. In fact, most of these studies define risk based on a collection of bivariate associations between the use of abciximab and various baseline characteristics (O'Donnell et al 1999, Plucinski et al 2000, Lucore et al 2001).



Differences in clinical practice patterns between institutions have also been observed. O'Donnell et al (1999) noted that the use of abciximab varied between 14% and 42% across six Michigan hospitals. Closer to home, a survey of Canadian cardiac catheterization centres also noted that utilization of this agent varies greatly both between and within provinces (Paradiso-Hardy et al 1999).

In terms of outcomes, observational studies have generally found abciximab to benefit PCI patients. For instance, Plucinski et al (2000) examined in-hospital mortality rates for 1502 patients who had undergone PCI between 1995 and 1997, and noted substantial reductions of in-hospital mortality rates in patients who had received abciximab. However, the Plucinski study only measured in-hospital outcomes, and there was no evidence to suggest that these benefits would be observed at one year.

Lucore and colleagues (2001) examined long-term outcomes in 3758 elective PCI patients for the effects of abciximab on balloon angioplasty and stenting. Four treatment groups were compared: (1) PTCA alone, (2) stent alone, (3) PTCA + abciximab, and (4) stent + abciximab. At one-year, the combined endpoint of death or myocardial infarction was not significantly different across the four groups. However, revascularization rates were significantly lower in both stent groups compared to the PTCA groups. Notably, the current study did not examine the composite endpoint of death and myocardial infarction. And as such, the results may not be comparable.

When comparing the results of the current study to those of clinical trials, one must be quite cautious. Since patients in the clinical setting represent a much broader spectrum of coronary disease it may be unrealistic to



anticipate results similar to those of clinical trials. Earlier studies such as EPIC and EPILOG took place before the introduction of stents, and thus, are not applicable to the population of the current study since 2330 (84.7%) of the 2751 patients had undergone coronary stenting (EPIC Investigators 1994, EPILOG Investigators 1997). As such, the patients in the EPISTENT trial may most closely resemble those of the current study (EPISTENT Investigators 1999). Briefly, the EPISTENT trial enrolled 2399 patients undergoing urgent or elective PCI and were randomized to one of three treatment arms: (1) stent + placebo, (2) stent + abciximab, and (3) angioplasty + abciximab. At one year, stenting with abciximab, compared to stenting alone, was coupled with improved survival. Notably, the combination of stenting and abciximab did not significantly reduce the rate of target vessel revascularization (CABG or PCI) compared to stenting alone; however, patients who had received only stents did undergo significantly fewer revascularization procedures compared to those who received angioplasty and abciximab.

### 8.3 STRENGTHS AND LIMITATIONS OF THE CURRENT STUDY

The current study has several strengths and limitations. Typically, prospective cohort studies can be plagued by high loss-to-follow-up rates (Hennekens and Buring 1987). Fortunately, this weakness was not considered to be a severe threat to the validity of the current study. When a patient gives consent to be enrolled in the APPROACH project, links to data from the Alberta Bureau of Vital Statistics and to hospital separation data are established. Due to the nature of the outcome, death was assumed to be accurately and completely recorded. Hospital separation data are used to ascertain subsequent admissions. However, there is a chance that some revascularization procedures may not have been recorded if a patient had a procedure performed outside of Alberta.





Although the ‘enhanced’ version of the data was obtained from the APPROACH Investigators, there was still a significant amount of missing data for certain clinical variables, such as ejection fraction. And as such, the validity of the study may have been threatened. Ideally, these data should be further ‘enhanced’ via the linkage to an alternative source of clinical data. However, this option was not viable in the current study.

The APPROACH project does not collect clinical information to the same extent as clinical trials. For instance, more comprehensive diagnostic information such as electrocardiogram results (i.e. ST-segment changes) and biomarker levels (i.e. CK, CK-MB, troponins I and T) may enhance the precision of risk stratification of patients. In addition, the rates of myocardial infarction and complications (i.e., bleeding etc.) after PCI are routinely assessed in clinical trials. These outcomes may have provided a more comprehensive view of the effects of this therapy in clinical practice.

Another important limitation of this study may be the presence of ‘treatment assignment bias’. Randomized clinical trials can eliminate this bias via the randomization of patients. The investigators of observational studies, however, have no control over the treatment assignment of patients. Treated and non-treated patients may differ significantly in their baseline characteristics, which may lead to biased estimates of the treatment effect. Although traditional methods of adjusting for these differences were carried out in this study, some methodologists suggest that these methods alone may not be effective (D’Agostino 1998, Drake and Fisher 1995). To adjust for this bias, the propensity score technique was suggested. A propensity score is defined as the conditional exposure probability given a set of independent predictors and is used to balance the covariates in the two groups, thereby reducing the treatment bias (Drake and Fisher 1995).



## 8.4 CONCLUSIONS

In Alberta, the use of abciximab was not associated with the risk of death or revascularization within one year of PCI. Patterns of abciximab use differed between institutions. The administration of abciximab did not significantly reduce the risk of death or revascularization within one year of PCI.

### *8.4.1 Implications*

The assessment of the utilization and effects on clinical outcomes of abciximab may impact future clinical practice. Despite abciximab's glowing track record in the clinical trials, its expense is limiting factor in its utilization in clinical practice, especially outside of the United States (Velianou et al 1999). In fact, a significant proportion of high-volume PCI centres in Canada have adopted a strategy to limit its use to patients in whom complications of PCI are expected or realized in order to control the cost of this therapy (Cardiac Care Network of Ontario 1998, as cited in Velianou et al 1999). Specifically, a provincial strategy was introduced in 1997 to concentrate its use in high-risk patients undergoing PCI, and funding was supplied for its use in 25% of all PCI procedures in Alberta (Muzyka 2001). As the current study illustrated, all three institutions exceeded this recommended ceiling, and considerable inter-institutional variation exists. Obviously, the 1997 recommendations are obsolete, and as a result of this study, the development of new clinical practice guidelines maybe encouraged.

### *8.4.2 Recommendations*

Several recommendations for future research are proposed. Firstly, missing data on clinically important variables such as ejection fraction may have influenced the results of the current study. Therefore, alternative techniques of dealing with missing data, such as data enhancement,



should be explored. Secondly, further investigation of the propensity score method is warranted in order to determine the presence or effect of treatment selection bias.

The analysis of these data at the physician level may clarify the nature of the inter-institutional variations. Data from hospital formularies or medical records on the dosage of abciximab administered may be useful to compare actual clinical practice to clinical trial protocols.

The economic and patient perspectives should also be considered when evaluating abciximab in the clinical setting. The quality of life measures will provide insight on patients' lives after this treatment, while a cost-effectiveness study will gauge the impact of this therapy on health care resources.

And finally, two intravenous GP IIb/IIIa inhibitors, eptifibatide and tirofiban, are in the early stages of use in clinical practice. Apart from their recognized efficacy, these agents are markedly lower in cost. Therefore, it would be interesting to document the trends in utilization and effectiveness of all three GP IIb/IIIa inhibitors as the less expensive agents come on board.

Due to these methodological concerns, recommendations to clinical practice and policy are premature and are reserved at this time.



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## APPENDIX I : APPROACH STUDY PROTOCOL



The Alberta Provincial Project for Outcome  
Assessment in Coronary Heart Disease

Principle Investigator: Dr. M.L. Knudtson  
Study Protocol  
Revised 9/22/00



## **Definition of Terms**

Work Status: 1=Full time, 2= Part time, 3=Unemployed, 4= Sick leave, 5=Retired, 6=Homemaker.

Occupation: Document the most recent occupation. Be as specific as possible in relation to the employment – do not state the name of the employer.

Quality of Life: The patient's own estimation of the state of his/her health rated on a scale of 1-10 (1=poor & 10=excellent).

### **CCS Class:**

- 0 No angina pectoris.
- I Ordinary physical activity, such as walking and climbing stairs, does not cause angina pectoris. Angina pectoris with strenuous, rapid or prolonged exertion.
- II Slight limitation of ordinal activity. Angina pectoris with walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, in wind, or when under emotional stress, or only during the few hours after awakening.
- III Marked limitation of activity. Angina pectoris with walking one or two blocks or climbing more than one flight of stairs in normal conditions.
- IVa Unstable angina pectoris, pain resolved with intensified medical therapy, now stable on oral medication. Inability to carry out any physical activity without discomfort- anginal syndrome may be present at rest.
- IVb Unstable angina pectoris on oral therapy, symptoms improved but angina pectoris with minimal provocation.
- IVc Symptoms persisting, not manageable on oral therapy, may be hemodynamically unstable, require coronary care monitoring and parenteral medication.

### **Atypical Pain**

Patient is experiencing atypical symptoms of angina pectoris.

(Primary source: Campeau L. The grading of angina pectoris. Circulation 1976;54(3):522-523.)

## **Outcome Determinants**

Renal insufficiency: Patient has a history of renal insufficiency diagnosed and/or treated by a physician. Specify if at baseline the patient is on dialysis or the creatinine is >200 µmol/L.



Congestive Heart Failure: Patient has a history of congestive heart failure diagnosed and/or treated by a physician. There must be a history of one or more of the following: exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea (PND), and either cardiac rales, or pulmonary congestion on x-rays. Neither edema nor dyspnea qualifies.

Prior infarction: Patient has a clear-cut history and enzyme documentation or typical ECG changes.

Hypertension: Patient has a history of hypertension diagnosed and/or treated by a physician.

Hyperlipidemia: Patient has a history of hyperlipidemia diagnosed and/or treated by a physician (total cholesterol >5.2 mmol/L, or HDL cholesterol <0.8mmol/L).

Diabetes mellitus: Patient has a history of diabetes mellitus diagnosed and/or treated by a physician.

Type I (insulin-dependent diabetic): There should be a history of 2 of the following diabetic ketoacidosis, juvenile onset and insulin use within 2 years of the diagnosis (if patient is not obese).

Type II (insulin-dependent): All other diabetes on insulin. Usually secondary onset in overweight patients.

Type II (non-insulin dependent): All type II diabetics not treated with insulin. May be diet or medication controlled.

Smoking:

A. Patient has smoked cigarettes (cigar and pipes excluded) in the preceding 3 months.

B. Patient has not smoked cigarettes (cigar and pipes excluded) in the preceding 3 months.

C. Patient has never smoked cigarettes (cigar and pipes excluded) in the preceding 3 months.

Family History: First-degree relatives (parents, siblings, or children: not grandparents, uncles, aunts) has diagnosed coronary artery disease (myocardial infarction, angina pectoris or requirement of a revascularization procedure (CABG/PTCA) before 60 years old. Unexplained sudden death is considered a manifestation of coronary artery disease. If the patient is adopted or does not know, record as unknown. (No longer collected.)





Prior thrombolytic therapy: Patient has received streptokinase, urokinase, APSAC, +/- rtPA within past 3 months.

Prior CABG: any previous CABG's regardless of location.

Prior PTCA: any previous PTCA's regardless of location.

Peripheral vascular disease: Typical symptoms of intermittent claudication or prior corrective surgery.

Comorbidity factors: The presence of pulmonary, liver and/or GI disease or malignancy if the disease interferes with quality of life and is likely to significantly limit life expectancy.

## **Indications for PCI**

Myocardial infarction: (Hospital admission → Discharge)

- A) *Direct PTCA*: first line of treatment (within 6 hours).
- B) *Cardiogenic Shock*: Systolic BP < 90mmHg for > 30 minutes. Not responsive to fluid resuscitation alone. Felt to be secondary to cardiac dysfunction and associated to signs of hypoperfusion and evidence of pulmonary venous congestion.
- C) *Persistent or recurrent ischemia <12 hrs*: symptoms and/or ECG changes thought by the physician to represent myocardial ischemia.
- D) *Recurrent ischemia >12hrs*: symptoms and/or ECG changes thought by the physician to represent myocardial ischemia.
- E) *Positive pre-discharge ETT*: as diagnosed by a physician as strongly positive. (>2mm ST depression or fall in blood pressure in stage 1).
- F) *Non-Q wave infarction*.
- G) *Confirm anatomy*: Patient is pain-free post infarction. Angiogram to determine further treatment or prognosis.
- H) *Positive pre-discharge ETT*: as diagnosed by a physician and is in the strongly positive category.

Post Infarction (Discharge < 6 weeks):

- A. Angina pectoris: mark 'yes' if patient complains of post-infarction angina within 6 weeks of discharge.
- B. Positive ETT: strongly positive category.
- C. Asymptomatic non-Q wave infarction.
- D. Asymptomatic Q wave infarction.



Unstable angina (with ECG changes):

- A) ST depression >1mm
- B) T wave inversion
- C) Indeterminant ECG
- D) No data available

Unstable angina (without ECG changes):

- A) Known coronary artery disease
- B) No known coronary artery disease

Prior PTCA: Clinical restenosis (return of symptoms or objective evidence of ischemia in dilated region) but not qualifying under the unstable angina category.

Prior CABG: Suspected graft problem. Early return of symptoms or objective evidence of ischemia in bypassed region(s).

Stable Angina:

- A) Medical failure: To include: (1) adequate doses of 3 categories of anti-anginal drugs; (2) patient intolerance to medication; (3) patient unable or unwilling to take medications (include patients whose jobs precludes taking medications).
- B) Positive ETT: Test called positive for ischemia by physician performing test.
- C) Strongly positive ETT: Fall in blood pressure or >2mm ST depression in Stage 1 (Bruce).
- D) Positive nuclear test
- E) Positive stress echo
- F) Need to know anatomy

Serious Arrhythmia: Sustained ventricular tachycardia or prior cardiac arrest/defibrillation/sudden death.

Silent Ischemia

Congestive Heart Failure: Prior documentation of CHF.

Protocol Study: Investigation dictated by protocol, not patient's clinical circumstances.



## **Atypical Symptoms - Confirm Anatomy**

### Extent of Coronary Artery Disease (Duke Coronary Index):

This will be scored according to the following index:

- 1) Disease less than 50%
- 2) 1 vessel disease (50-75%)
- 3) 1 vessel disease (95%)
- 4) 2 vessel disease
- 5) 2 vessel disease (Both 95%)
- 6) 1 vessel disease (95% Prox. LAD)
- 7) 2 vessel disease (95% LAD)
- 8) 2 vessel disease (95% Prox. LAD)
- 9) 3 vessel disease
- 10) 3 vessel disease (1 95%)
- 11) 3 vessel disease (Prox LAD)
- 12) 3 vessel disease (95% Prox LAD)
- 13) Left Main disease
- 14) Severe Left Main disease (>75%)

## **Procedure Selection Factors**

Lower Procedural Risk Expected: Although other procedures may be possible, the selected procedure was felt to carry to lowest procedural risk.

More Complete Revascularization Possible: The selected procedure will achieve a greater degree of revascularization than other options. In the case of PTCA this may be because of small distal vessel size or distal disease; with CABG this may include total occlusions, or complex diffuse proximal disease.

Culprit lesion known: Culprit lesion PTCA is expected to stabilize patient and/or render him/her asymptomatic.

Patient an IMA candidate: Patient is a good candidate for internal mammary artery grafting and better long-term result expected than with PTCA.

Patient staging possible: This applies to PTCA only. Although patient had multi-vessel disease, the procedure can be staged if necessary to control procedure risk.

Small or diseased distal vessel: Factors that usually preclude a good surgical result, i.e., factors in favour of PTCA and against CABG.



Complex lesion morphology: Usually type 'C' lesions. Factors that favour CABG over PTCA.

Published trial results: Although other approaches may be possible, it is the interventionalists/surgeons opinion that published trial support this decision.

Number of diseased vessels: This should be selected if the number of diseased vessels in the subject case strongly influenced the type of revascularization procedure selected e.g., PTCA and single vessel disease.

Vascular Access Problems: Problems expected in angioplasty device insertion played a role in the selection of CABG.

Previous Surgery: Patient has had a prior bypass surgery. The risk of repeat surgery favours angioplasty.

Previous Angioplasty (Restenosis): patient is a good candidate for surgery and has had 2 or more previous angioplasties.

Age: In many cases, the younger patients (in anticipation of later disease progression) and older patients (in view of higher procedural risk) are selectively referred for angioplasty. This is not always the case where gains outweigh increased risk and where complete revascularization by 'arterial revascularization' (IMA or gastroepiploic grafts) is possible in younger patients.

Patient preference: Patients prefer a specific type of revascularization.

Psychosocial/economic: The revascularization procedure is expected to increase the likelihood that the patient can return to a more personally rewarding lifestyle even though there is no other important driving force in the decision.

Other: Includes special circumstances where revascularization is felt desirable despite other established reasons for this decision. This may include angiographic by asymptomatic restenosis where PTCA is performed to improve the level of flow in anticipation of future need in young people or in those with rapidly progressive disease.





Parsonnet Score: (Parsonnet V, Dean D, Bernstein AD: A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. Circulation 1989;79(suppl I): I-3-I-12.)  
The surgical groups in the Province of Alberta are developing a modified risk assessment index that may be used instead.

Procedure data:

PTCA: The segments that were dilated will be documented according to the Heartview® computer software program.  
CABG: The vessels grafted and type of graft inserted will be documented. IMA= internal mammary artery, SVG=saphenous vein graft, GE=gastroepiploic.

Equipment used (PTCA): Intended to track newer technology use (a) perfusion balloon; (b) DCA, directional atherectomy; (c) other atherectomy, i.e., rotational; (d) stent; (e) other.

Complete revascularization: Confirm with interventionalist/surgeon that there are not vessels > 1.5mm diameter left with lesions>70% in proximal or mid-portion of main arterial trunk of LAD or dominant RCA or LCx.

Endarterectomy needed: If endarterectomy done during surgery the vessels will be listed.



**Form 3 (PTCA)**

DATE OF ANGIOPLASTY: \_\_ \_\_ \_\_ (DD/MMM/YY) CINE NUMBER: \_\_

INTERVENTIONALIST: \_\_\_\_\_

WORK STATUS \_\_\_\_\_ (1. Full Time 2. Part Time 3. Unemployed  
4. Sick Leave 5. Retired 6. Homemaker)

CCS Class 0 \_\_ I \_\_ II \_\_ III \_\_ IV a \_\_ IV b \_\_ IV c \_\_ Atypical \_\_

PROCEDURE SCHEDULING: DIRECT \_\_ STAGGED \_\_ PLANNED \_\_

PRIORITY: EMERGENCY \_\_ URGENT IN \_\_ URGENT OUT \_\_  
ELECTIVE \_\_

INDICATION (check one)	Y	N	INDICATION (check one)	Y	N	INDICATION (check one)	Y	N
Recurrent pain/ abrupt closure post-PTCA			Asymptomatic Q wave infarction			Positive non- invasive test		
Myocardial infarction (in- hospital)			Unstable angina with ECG changes			Need to know anatomy		
Direct PTCA candidate			ST depression >1mm			Serious Arrhythmia/ Sudden death		
Cardiogenic Shock			T wave inversion			Evidence for ischemia		
Recurrent Ischemia (<12 hrs)			Indeterminate ECG			Other		
Recurrent Ischemia (>12 hrs)			No data available			Silent ischemia		
Positive pre- discharge exercise test			UA without ECG changes			LV dysfunction		
Asymptomatic critical anatomy			Known CAD			Q-wave infarction		
Post-infarction (discharge to 6 weeks)			No known CAD			Inferior/posterior		
Angina			Prior PTCA			Anterior/Lateral		
Positive exercise test			Prior CABG			LBBB		
Asymptomatic Non-Q wave infarction			Stable angina Medical failure			Unreadable ECG		



# PROCEDURE SELECTION FACTORS & OUTCOME DETERMINANTS

FACTOR	Y	N	ITEM	?	Y	N
High surgical risk			Renal insufficiency			
Lesion more suitable to PTCA			Dialysis			
Single vessel disease			Creatinine > 200 umol/L			
Restenosis lesion			Congestive heart failure			
Lesion or clinical instability			Prior infarction			
Medical treatment failure			Hypertension			
Suitable-culprit lesion approach			Hyperlipidemia			
Age extremes			Diabetes mellitus			
Published clinical trials			Type I			
Occupation considerations			Type II (insulin-dep)			
Psychosocial considerations			Type II (non-insulin-dependent)			
Patient preference			Peripheral vascular disease			
Complications-NONE			Cerebrovascular disease			
Complete revascularization			Smoking- Ever			
No-by intention			- within last 3 months			
No-staging planned/eval			- within last 3 years			
No-due to PTCA failure			Family history of CAD			
Death			Prior thrombolytic therapy			
MI-non-Q-wave			Prior PTCA			
MI-inferior/posterior			Prior CABG			
-Anterior/lateral			Comorbidity factors			
Emergency CABG			Pulmonary			
Abrupt Closure			Liver/GI			
Angiographic failure			Malignancy			

## PROCEDURE DATA

Guiding Caths	#	Directional atherectomy	#	IVUS	#	Balloons	#	Rotational atherectomy	#
Perfusion balloons	#	Stents	#	Other	#	Amount of dye		CC's	
Ejection Fraction (check one or write %)		<30%		30-50%		>50%		Not done due to instability	
Type of dye (check one)		Non-ionic		Ionic		Low ionic			



# APPENDIX II: LOGISTIC REGRESSION MODELS PREDICTING DEATH WITHIN ONE-YEAR OF THE INDEX PCI.

## CURRENT MODEL

### Univariate Analyses:

Table All.1. Univariate relationship between patient demographics, comorbidities and death within one year of the index PCI. (n=2751)

Variable	% of Patients	% of Outcomes	OR	95%CI	p-value*
Demographics					
Age	--	--	1.086	1.063,1.110	0.000
Age					
>75 years	84.7	2.3	1.000		
≥75 years	15.3	9.7	4.633	3.038, 7.063	0.000
Sex					
Male	74.7	3.0	1.000		
Female	25.3	4.6	1.546	1.000,2.390	0.050
Comorbidities					
COPD					
No	89.6	3.1	1.000		
Yes	10.4	5.9	1.952	1.137,3.349	0.015
CEVD					
No	93.5	3.1	1.000		
Yes	6.5	7.9	2.660	1.475,4.796	0.001
Renal dysfunction					
No	97.2	3.0	1.000		
Yes	2.8	16.7	6.399	3.391, 12.08	0.000
Dialysis					
No	98.6	3.4	1.000		
Yes	1.4	7.7	2.400	0.726, 7.938	0.151
Diabetes					
No	79.6	3.1	1.000		
Yes	20.4	4.8	1.606	1.017, 2.535	0.042
Hyperlipidemia					
No	36.3	6.3	1.000		
Yes	63.7	1.8	0.267	0.173,0.414	0.000
Hypertension					
No	47.0	3.3	1.000		
Yes	53.0	3.5	1.052	0.696, 1.590	0.809
Liver/GI					
No	95.6	3.2	1.000		
Yes	4.4	8.3	2.730	1.380, 5.404	0.004
Malignancy					
No	96.0	3.3	1.000		
Yes	4.0	6.4	1.995	0.901, 4.417	0.089
PVD					
No	94.3	3.3	1.000		
Yes	5.7	5.7	1.782	0.879, 3.613	0.109
Present smoker					
No	69.5	3.9	1.000		
Yes	30.5	2.3	0.569	0.342,0.947	0.030





Variable	% of Patients	% of Outcomes	OR	95%CI	p-value*
Past smoker					
No	62.1	3.7	1.000		
Yes	37.9	2.9	0.761	0.490, 1.182	0.224

\*, p-value of the likelihood ratio chi-square test, CI= Confidence Intervals, LL= lower limit; UL=upper limit.

Table AII.2 Univariate relationships between prior, admission cardiac events and death within one year of the index PCI. (n=2751).

Variable	% of Patients	% of Outcomes	OR	95%CI	p-value
<b>Prior Cardiac Events</b>					
History of CHF					
No	87.2	2.2	1.000		
Yes	12.8	11.9	6.115	4.004, 9.340	0.000
Prior MI					
No	35.6	1.4	1.000		
Yes	64.4	4.5	3.254	1.834, 5.772	0.000
Prior CABG					
No	90.2	3.1	1.000		
Yes	9.8	5.9	1.949	1.121, 3.389	0.018
Prior PTCA					
No	83.9	3.5	1.000		
Yes	16.1	2.9	0.829	0.457, 1.502	0.536
Prior thrombolytic therapy					
No	91.2	3.3	1.000		
Yes	8.8	1.7	0.453	0.165, 1.243	0.124
<b>Cardiac Events on Admission</b>					
MI on admission					
No	53.4	2.0	1.000		
Yes	46.6	5.1	2.652	1.701, 4.136	0.000
Cardiogenic shock					
No	98.9	3.2	1.000		
Yes	1.1	24.1	9.636	4.009, 23.16	0.000
CCS Class					0.000
0	1.7	2.1	Ref		
I	2.0	1.8	0.870	0.053,14.302	0.923
II	11.8	0.9	0.438	0.045,4.299	0.479
III	11.7	3.1	1.506	0.189,12.038	0.699
IV A	32.6	2.0	0.961	0.126, 7.356	0.970
IV B	8.0	4.1	2.014	0.249,16.286	0.511
IV C	14.2	6.7	3.357	0.445,25.314	0.240
Atypical	1.4	2.1	2.541	0.222,29.113	0.454
Missing	16.5	25.5	2.617	0.346,19.787	0.351

\*, p-value of the likelihood ratio chi-square test, CI= Confidence Intervals, LL= lower limit; UL=upper limit.



Table All.3 Univariate relationships between coronary anatomy and death within one year of the index PCI. (n=2751).

Variable	% of Patients	% of Outcomes	OR	95%CI	p-value
<b>Coronary Anatomy</b>					
# lesions >70% stenosis			1.237	1.114, 1.372	0.000
Graft					
No	91.9	3.3	1.000		
Yes	8.1	4.9	1.521	0.798, 2.896	0.202
Pre-PCI PLAD					
No	75.8	3.2	1.000		
Yes	24.2	4.2	1.340	0.853, 2.103	0.204
Pre-PCI LMAIN					
No	97.6	3.4	1.000		
Yes	2.4	6.0	1.830	0.652, 5.137	0.251
Ejection Fraction					0.000
>50%	25.7	0.7	Ref		
30-50%	15.4	3.1	4.438	1.572, 12.53	0.005
<30%	2.0	23.2	42.314	14.43, 124.08	0.000
Not done (instability)	14.9	4.6	6.819	2.528, 18.39	0.000
Missing	42.1	3.8	5.533	2.185, 14.01	0.000

\*, p-value of the likelihood ratio chi-square test, CI= Confidence Intervals, LL= lower limit; UL=upper limit.

Table All.4 Univariate relationships between procedural factors and death within one year of the index PCI. (n=2751).

Variable	% of Patients	% of Outcomes	OR	95%CI	p-value
<b>Procedural Factors</b>					
Priority					0.000
Emergency	13.1	7.2	Ref		
Urgent in	39.6	2.2	0.290	0.164, 0.513	0.000
Urgent out	6.2	1.2	0.153	0.036, 0.654	0.011
Planned	17.2	2.7	0.364	0.184, 0.719	0.004
Missing	23.9	4.4	0.594	0.344, 1.025	0.061
Direct procedure					
No	54.7	1.9	1.000		
Yes	45.3	5.2	2.801	1.796, 4.368	0.000
IABP					0.000
No	89.6	2.8	Ref		
Yes	1.9	28.8	13.869	7.274, 26.44	0.000
Missing	8.5	3.8	1.368	0.675, 2.776	0.385
Stent					
No	15.3	4.5	1.000		
Yes	84.7	3.2	0.704	0.421, 1.177	0.181
No of stents used	--	--	0.974	0.771, 1.230	0.823
Abciximab					
No	56.5	2.8	1.000		
Yes	43.5	4.2	1.493	0.989, 2.256	0.057
Complete revascularization					
No	47.5	5.0	1.000		
Yes	52.5	2.0	0.392	0.251, 0.610	0.000



Variable	% of Patients	% of Outcomes	OR	95%CI	p-value
Hospital					
A	55.6	2.6	Ref		0.012
B	23.8	3.7	1.416	0.847, 2.370	0.185
C	20.6	5.3	2.084	1.285, 3.380	0.003

\*, p-value of the likelihood ratio chi-square test, CI= Confidence Intervals, LL= lower limit; UL=upper limit.

### Multivariate Analyses:

Table AII.5. Full multivariate model predicting death within one year of the index PCI (n=2751).

Variable	OR	95% LL	95% UL	p-value
Age	1.058	1.031	1.085	0.000
Sex	1.218	0.728	2.036	0.453
COPD	1.462	0.762	2.803	0.253
CEVD	1.485	0.720	3.059	0.284
Renal dysfunction	1.710	0.744	3.934	0.207
Diabetes	1.355	0.789	2.327	0.270
Hyperlipidemia	0.401	0.242	0.667	0.000
Liver/GI disease	2.317	1.007	5.332	0.048
Malignancy	0.908	0.343	2.408	0.846
PVD	1.131	0.485	2.634	0.776
Prior lytic therapy	0.328	0.102	1.058	0.062
Present smoker	0.991	0.526	1.865	0.977
Old smoker	0.984	0.581	1.666	0.952
MI on admission	0.013	0.000	8.49*10 <sup>5</sup>	0.637
CHF	1.754	1.020	3.016	0.042
Prior MI	1.955	0.929	4.112	0.077
Prior CABG	4.022	1.513	10.696	0.005
Cardiogenic shock	1.886	0.583	6.099	0.289
CCS Class				
0	Ref.			0.207
I	2.682	0.142	50.685	0.511
II	0.936	0.084	10.428	0.957
III	2.539	0.285	22.623	0.404
IV a	1.224	0.143	10.486	0.854
IV b	2.273	0.239	21.587	0.475
IV c	1.852	0.206	16.663	0.583
Atypical	3.349	0.224	49.994	0.381
Missing	3.527	0.418	29.756	0.247
# lesions >70% stenosis	1.108	0.944	1.300	0.208
Graft	0.433	0.134	1.394	0.160
Pre-PCI PLAD	0.865	0.505	1.482	0.598
Pre-PCI Left main	0.311	0.087	1.116	0.073
LVEF				
>50%	Ref.			0.000
30-50%	2.467	0.818	7.445	0.109
<30%	16.026	4.837	53.100	0.000
Not done	4.101	1.401	12.008	0.010
Missing	3.805	1.410	10.267	0.008
Priority				



Variable	OR	95% LL	95% UL	p-value
Emergency	Ref.			0.111
Urgent In	0.419	0.199	0.885	0.022
Urgent Out	0.261	0.051	1.330	0.106
Planned	0.678	0.271	1.699	0.407
Missing	0.840	0.409	1.725	0.635
Complete revascularization	0.737	0.425	1.278	0.278
Direct procedure	98.797	0.000	6.31*10 <sup>9</sup>	0.616
IABP				
No	Ref.			0.032
Yes	3.326	1.353	8.174	0.009
Missing	1.090	0.472	2.517	0.840
Stent	0.675	0.367	1.244	0.208
Constant	0.000			0.000

\*, p-value of the likelihood ratio chi-square test, CI= Confidence Intervals, LL= lower limit; UL=upper limit.

Table AII.6 Model building process for the model predicting death within one year of the index PCI.

Variable	-2 LogLikelihood	Likelihood ratio test statistic	Df	p-value
Constant	819.518			
Full Model	579.959	239.559	43	0.000
Present smoker	579.960	0.001	1	0.997
Past smoker	579.963	0.003	1	0.956
Malignancy	580.001	0.038	1	0.846
PVD	580.078	0.078	1	0.781
Prox-LAD	580.353	0.275	1	0.600
Sex	580.949	0.596	1	0.440
Cardiogenic shock	582.022	1.073	1	0.300
Complete revascularization	583.073	1.051	1	0.305
CEVD	584.436	1.363	1	0.243
Diabetes	585.796	1.360	1	0.244
MI on admission	587.415	1.619	1	0.203
Direct procedure	588.413	0.999	1	0.318
COPD	590.216	1.803	1	0.179
Stent	592.323	2.107	1	0.147
CCS Class	603.776	11.453	8	0.177
Graft	605.645	1.869	1	0.172
# lesions >70% stenosis	607.434	1.789	1	0.181

Df=degrees of freedom.



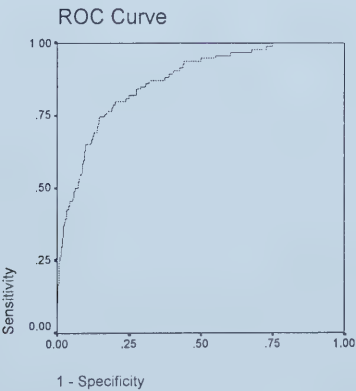


Table All.7 Final multivariate model for predicting death within one year of the index PCI. Hosmer-Lemeshow Goodness-of-Fit statistic=3.036 (df=8,p=0.932).

Variable	OR	95% LL	95% UL	p-value
Age	1.065	1.040	1.090	0.000
Renal dysfunction	2.194	1.004	4.797	0.049
Hyperlipidemia	0.430	0.264	0.700	0.001
Liver/GI disease	2.416	1.085	5.379	0.031
Prior lytic therapy	0.324	0.107	0.983	0.047
CHF	2.245	1.358	3.711	0.002
Prior MI	2.238	1.197	4.185	0.012
Prior CABG	2.502	1.334	4.693	0.004
Pre-PCI Left main	0.371	0.112	1.232	0.105
LVEF				
>50%	Ref.			0.000
30-50%	2.433	0.829	7.146	0.106
<30%	12.819	4.018	40.905	0.000
Not done	4.144	1.463	11.741	0.007
Missing	4.375	1.670	11.461	0.003
Priority				
Emergency	Ref.			0.047
Urgent In	0.367	0.188	0.718	0.003
Urgent Out	0.272	0.059	1.258	0.096
Planned	0.550	0.251	1.209	0.137
Missing	0.671	0.351	1.280	0.226
IABP				
No	Ref.			0.006
Yes	3.790	1.657	8.670	0.002
Missing	1.339	0.616	2.910	0.461
Constant	0.000			0.000

\*, p-value of the likelihood ratio chi-square test, CI= Confidence Intervals, LL= lower limit; UL=upper limit.

Figure All.1. ROC curve for the model predicting death within one year of the index PCI (n=2751). C-statistic=0.868; p=0.000; 95%CI (0.832, 0.904)





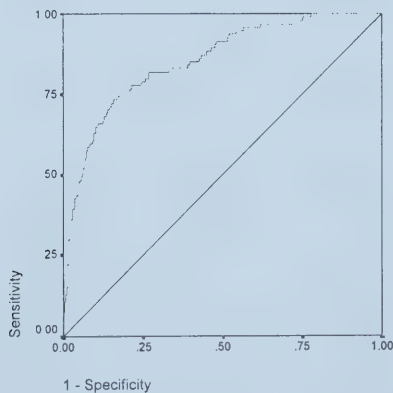
KAUL MODEL

Table All.8. Kaul model predicting death within one year of index PCI (n=2751). Hosmer-Lemeshow Goodness-of-Fit=10.44; df=8; p=0.235.

Variable	OR	95% LL	95% UL	p-value
Age ≥ 75 years	<b>2.806</b>	1.745	4.513	0.000
CHF	<b>2.564</b>	1.558	4.221	0.000
COPD	1.376	0.740	2.559	0.313
Dialysis	1.342	0.375	4.802	0.651
Hyperlipidemia	0.409	0.254	0.657	0.000
Malignancy	1.150	0.445	2.973	0.774
PVD	1.458	0.682	3.118	0.331
Cardiogenic shock	2.540	0.837	7.713	0.100
Ejection Fraction				
> 50%	ref.			0.000
30-50%	<b>3.019</b>	1.039	8.777	0.042
< 30%	<b>15.617</b>	4.888	49.896	0.000
Not done	<b>4.570</b>	1.633	12.786	0.004
Missing	<b>4.669</b>	1.814	12.019	0.001
# Lesions >70% stenosis				
>2	1.528	0.922	2.532	0.100
Prox. LAD	0.905	0.544	1.507	0.703
Lft. Main	0.416	0.123	1.404	0.158
IABP	<b>4.053</b>	1.805	9.098	0.001
Emergent procedure	<b>1.755</b>	1.007	3.058	0.047
Complete revascularization	0.661	0.390	1.119	0.123
Constant	0.007			0.000

\*, p-value of the likelihood ratio chi-square test, CI= Confidence Intervals, LL= lower limit; UL=upper limit.

Figure All.2. ROC curve for the Kaul model (n=2751). C-statistic=0.853  
95%CI (0.813, 0.893)





# **APPENDIX III: LOGISTIC REGRESSION MODELS PREDICTING REPEAT REVASCULARIZATION WITHIN ONE YEAR OF PCI**

## CURRENT MODEL

### *Univariate Analyses:*

Table AIII.1. Univariate relationships between patient demographics, comorbidities and revascularization (re-PCI or CABG) within one year of the index PCI using logistic regression (n=2665).

Variable	Patients (%)	Outcomes (%)	OR	95%CI	p-value
<b>Demographics</b>					
Age			0.989	(0.980, 0.998)	0.013
Age					
< 75 years	85.7	17.0	1.000	Ref.	
≥75 years	14.3	11.6	0.638	(0.457, 0.889)	0.008
Sex					
Male	75.0	15.7	1.000	Ref.	
Female	25.0	17.9	1.169	(0.927, 1.474)	0.188
<b>Comorbidities</b>					
COPD					
No	89.8	16.5	1.000	Ref.	
Yes	10.2	14.4	0.857	(0.600, 1.223)	0.395
Cerebravascular disease					
No	93.8	16.3	1.000	Ref.	
Yes	6.2	15.2	0.922	(0.594, 1.430)	0.717
Renal dysfunction					
No	97.6	16.2	1.000	Ref.	
Yes	2.4	18.5	1.171	(0.620, 2.210)	0.627
Diabetes					
No	79.9	16.1	1.000	Ref.	
Yes	20.1	16.9	1.058	(0.821, 1.365)	0.661
Hyperlipidemia					
No	35.2	17.1	1.000	Ref.	
Yes	64.8	15.8	0.909	(0.734, 1.125)	0.380
Hypertension					
No	47.0	16.2	1.000	Ref.	
Yes	53.0	16.3	1.012	(0.823, 1.244)	0.910
Liver/GI disease					
No	95.8	16.4	1.000	Ref.	
Yes	4.2	12.6	0.735	(0.415, 1.299)	0.289



Variable	Patients (%)	Outcomes (%)	OR	95%CI	p-value
Malignancy					
No	96.1	16.2	1.000	Ref.	
Yes	3.9	16.5	1.019	(0.599, 1.732)	0.945
PVD					
No	94.4	16.3	1.000		
Yes	5.6	15.4	0.937	(0.593, 1.479)	0.780
Present smoker					
No	69.2	16.7	1.000	Ref.	
Yes	30.8	15.3	0.898	(0.716, 1.127)	0.354
Past smoker					
No	61.9	15.6	1.000	Ref.	
Yes	38.1	17.3	1.127	(0.913, 1.391)	0.266

\*, p-value of the likelihood ratio chi-square test, CI= Confidence Intervals, LL= lower limit; UL=upper limit.

Table AIII.2 Univariate relationships between prior cardiac events, cardiac events upon admission and revascularization (re-PCI or CABG) within one year of the index PCI using logistic regression (n=2665).

Variable	Patients (%)	Outcomes (%)	OR	95%CI	p-value
<b>Prior Cardiac Events</b>					
History of CHF					
No	88.3	16.5	1.000	Ref.	
Yes	11.7	14.5	0.860	(0.616, 1.202)	0.378
Prior MI					
No	36.3	18.4	1.000	Ref.	
Yes	63.7	15.1	0.788	(0.639, 0.973)	0.027
Prior CABG					
No	90.5	15.8	1.000	Ref.	
Yes	9.5	20.9	1.416	(1.026, 1.954)	0.034
Prior PTCA					
No	83.8	15.9	1.000	Ref.	
Yes	16.2	18.3	1.191	(0.910, 1.558)	0.204
Prior thrombolytic therapy					
No	91.0	16.6	1.000	Ref.	0.158
Yes	9.0	13.0	0.754	(0.509, 1.116)	
<b>Cardiac Events on Admission</b>					
Cardiogenic shock					
No	99.2	16.3	1.000	Ref.	
Yes	0.8	13.6	0.812	(0.239, 2.756)	0.739





Variable	Patients (%)	Outcomes (%)	OR	95%CI	p-value
MI on Admission					
No	54.2	17.7	1.000	Ref.	
Yes	45.8	14.5	0.791	(0.642, 0.975)	0.028
CCS Class					
0	1.8	12.8	1.000	Ref.	0.060
I	2.0	7.4	0.547	(0.144, 2.069)	0.374
II	12.1	21.7	1.898	(0.774, 4.653)	0.161
III	11.7	17.3	1.430	(0.578, 3.537)	0.439
IV A	33.1	15.0	1.206	(0.502, 2.897)	0.675
IV B	7.9	17.6	1.461	(0.578, 3.694)	0.423
IV C	13.7	16.2	1.322	(0.537, 3.254)	0.544
Atypical	1.4	24.3	2.196	(0.703, 6.863)	0.176
Missing	16.2	14.2	1.127	(0.459, 2.767)	0.795
CCS Class >III					
No	33.5	16.8	1.000	Ref.	
Yes	66.5	16.0	0.939	(0.756, 1.166)	0.568

\*, p-value of the likelihood ratio chi-square test, CI= Confidence Intervals, LL= lower limit; UL=upper limit.

Table AIII.3 Univariate relationships between coronary anatomy and revascularization (re-PCI or CABG) within one year of the index PCI using logistic regression (n=2665).

Variable	Patients (%)	Outcomes (%)	OR	95%CI	p-value
<b>Coronary Anatomy</b>					
# lesions >70% stenosis			1.152	(1.083, 1.224)	0.000
>2 lesions >70% stenosis					
No	67.9	14.0	1.000	Ref.	
Yes	32.1	21.0	1.628	(1.317, 2.012)	0.000
Grafts					
No	92.0	15.9	1.000	Ref.	
Yes	8.0	19.8	1.305	(0.915, 1.861)	0.141
Prox. LAD					
No	76.0	15.9	1.000	Ref.	
Yes	24.0	17.5	1.128	(0.890, 1.428)	0.319
Lft. Main					
No	97.6	16.0	1.000	Ref.	
Yes	2.4	25.4	1.782	(1.001, 3.173)	0.050
Ejection Fraction					
>50%	1.6	16.4	1.000	Ref.	0.090
30-50%	15.4	20.5	1.313	(0.961, 1.794)	0.087
<30%	26.4	20.9	1.349	(0.630, 2.888)	0.441



Variable	Patients (%)	Outcomes (%)	OR	95%CI	p-value
Not done	14.7	14.9	0.890	(0.632, 1.255)	0.507
Missing	41.9	16.3	0.893	(0.689, 1.157)	0.393

\*, p-value of the likelihood ratio chi-square test, CI= Confidence Intervals, LL= lower limit; UL=upper limit.

Table AIII.4 Univariate relationships between procedural factors and revascularization (re-PCI or CABG) within one year of the index PCI using logistic regression (n=2665).

Variable	Patients (%)	Outcomes (%)	OR	95%CI	p-value
<b>Procedural Factors</b>					
Priority					
Emergency	12.6	15.8	1.000	Ref.	0.000
Urgent in	40.1	13.5	0.832	(0.591, 1.171)	0.292
Urgent out	6.3	19.0	1.252	(0.771, 2.032)	0.363
Planned	17.3	13.3	0.813	(0.546, 1.212)	0.310
Missing	23.7	22.6	1.551	(1.096, 2.197)	0.013
Emergent procedure	87.4	16.3	1.000	Ref.	0.816
No	12.6	15.8	0.964	(0.704, 1.318)	
Yes					
Complete revasc.					
No	46.7	20.5	1.000	Ref.	
Yes	53.3	12.6	0.559	(0.453, 0.689)	0.000
Direct procedure					
No	55.6	18.8	1.000	Ref.	
Yes	44.4	13.1	0.654	(0.528, 0.810)	0.000
IABP					
No	90.1	15.9	1.000	Ref.	0.188
Yes	1.4	24.3	1.704	(0.798, 3.641)	0.169
Missing	8.5	19.1	1.253	(0.883, 1.778)	0.207
Stent					
No	15.1	21.4	1.000	Ref.	
Yes	84.9	15.3	0.666	(0.511, 0.868)	0.003
Abciximab					
No	56.8	16.2	1.000	Ref.	
Yes	43.2	16.4	1.015	(0.825, 1.250)	0.886

\*, p-value of the likelihood ratio chi-square test, CI= Confidence Intervals, LL= lower limit; UL=upper limit.



*Multivariate Analyses:*

Table AIII.5 Full multivariate model predicting revascularization within one year of the index PCI (n=2665). All variables significant at p<0.25 in the univariate analysis entered.

Variable	OR	95% LL	95% UL	p-value
Age	0.980	0.970	0.989	0.000
Sex (female)	1.397	1.091	1.788	0.008
Prior thrombolytic therapy	0.944	0.614	1.451	0.793
MI on admission	8.596	4.154	17.787	0.000
Prior MI	0.720	0.545	0.951	0.021
Prior CABG	1.365	0.788	2.364	0.266
Prior PTCA	1.102	0.823	1.476	0.515
# lesions>70% stenosis	1.129	1.042	1.224	0.003
Graft	0.675	0.357	1.278	0.228
Pre-PCI LMAIN	1.326	0.697	2.521	0.390
LVEF				
>50%	1.000			0.064
30-50%	1.288	0.926	1.790	0.132
<30%	1.478	0.672	3.250	0.332
Not done	0.882	0.620	1.255	0.485
Missing	0.842	0.642	1.103	0.212
Complete revasc.	0.606	0.475	0.772	0.000
Direct procedure	0.095	0.047	0.193	0.000
IABP				
No	1.000			0.458
Yes	1.546	0.698	3.420	0.283
Missing	1.137	0.783	1.653	0.500
Stent	0.739	0.559	0.978	0.034
Constant	0.985			0.966

\*, p-value of the likelihood ratio chi-square test, CI= Confidence Intervals, LL= lower limit; UL=upper limit.



Table AIII.6. Model building process using backward stepwise logistic regression.

Variable	-2 Log Likelihood	Likelihood ratio test statistic	Df	p-value
Constant	2359.091			
Full model	2232.456	126.456	19	0.000
Prior thrombolytic therapy	2232.525	0.069	1	0.792
Prior PTCA	2232.951	0.425	1	0.514
IABP	2234.453	1.502	2	0.472
Left main disease	2235.357	0.905	1	0.342
Graft	2236.500	1.143	1	0.285
Prior CABG	2236.754	0.254	1	0.614

Df=degrees of freedom

Table AIII.7. Final multivariate model for revascularization at one-year. Hosmer-Lemeshow Goodness-of-Fit statistic= 8.214, df=8, p=0.413.

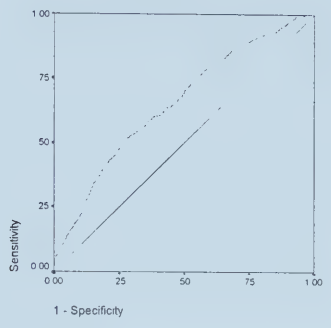
Variable	OR	95% LL	95%UL	p-value
Age	0.980	0.970	0.990	0.000
Sex (female)	1.388	1.085	1.776	0.009
MI on admission	8.589	4.167	17.704	0.000
Prior MI	0.728	0.554	0.956	0.022
# lesions>70% stenosis	1.128	1.051	1.212	0.001
LVEF				
>50%	1.000			0.065
30-50%	1.296	0.934	1.799	0.121
<30%	1.506	0.688	3.296	0.306
Not done	0.890	0.626	1.264	0.514
Missing	0.851	0.652	1.111	0.235
Complete revasc.	0.595	0.468	0.758	0.000
Direct procedure	0.094	0.046	0.191	0.000
Stent	0.726	0.552	0.956	0.022
Constant	1.021			0.952

\*, p-value of the likelihood ratio chi-square test, CI= Confidence Intervals, LL= lower limit; UL=upper limit.





Figure AIII.1. ROC curve of the current model predicting revascularization within one year (n=2665). C-statistic=0.654, 95% CI (0.626, 0.683), p=0.000



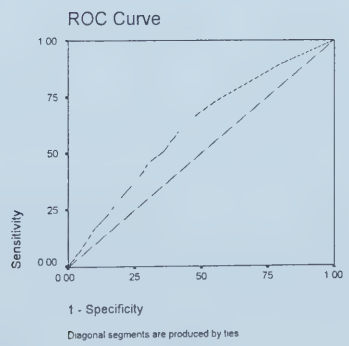
KAUL MODEL

Table AIII.8. Kaul model that predicts revascularization within one year of the index PCI (n=2665). Hosmer-Lemeshow Goodness-of-fit statistic=5.387 df=7, p=0.613.

Variable	OR	95% LL	95% UL	p-value
Sex (female)	1.188	0.939	1.503	0.151
Prior MI	0.758	0.612	0.938	0.011
>2 lesions >70%	1.381	1.093	1.745	0.007
Stent	0.725	0.554	0.949	0.019
Complete revasc.	0.642	0.509	0.809	0.000
Constant	0.318			0.000

\*, p-value of the likelihood ratio chi-square test, CI= Confidence Intervals, LL= lower limit; UL=upper limit.

Figure AIII.2. ROC curve of the Kaul model predicting revascularization within one year of PCI (n=2665). C-statistic=0.611, 95% CI (0.582, 0.639), p=0.000.

















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